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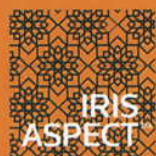
SMARTER NOT HARDER

ENDOCRINOLOGY



NOVAFY

INTERNAL MEDICINE



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In Capsule Series

Internal medicine

*Smarter, not
Harder!"*

Endocrinology

Dr. Ahmed Mowafy

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

لَا يُكَلِّفُ اللَّهُ نَفْسًا إِلَّا وُسْعَهَا لَهَا مَا كَسَبَتْ وَعَلَيْهَا مَا اكْتَسَبَتْ رَبَّنَا لَا تُؤَاخِذْنَا إِنْ
نَسِينَا أَوْ أَخْطَأْنَا رَبَّنَا وَلَا تَحْمِلْ عَلَيْنَا إَصْرًا كَمَا حَمَلْتَهُ عَلَى الَّذِينَ مِنْ قَبْلِنَا رَبَّنَا وَلَا
تَحْمِلْنَا مَا لَا طَاقَةَ لَنَا بِهِ وَاعْفُ عَنَّا وَاعْفِرْ لَنَا وَارْحَمْنَا أَنْتَ مَوْلَانَا فَانصُرْنَا عَلَى
الْقَوْمِ الْكَافِرِينَ

صدق الله العظيم

سورة البقرة (آية 286)

Preface

- *First and foremost, thanks are due to **ALLAH**, to whom I relate any success in achieving any work in my life.*
- *Great thanks to those who helped me, and greater thanks to those who try to break my wings as they make me more able to fly.*
- *My thanks are extended to all my medical students whom I produce this series "**In Capsule Series**" to obtain a higher degree in internal medicine by a simple effort.*
- *Finally, I wish to thank all members of My Family, my colleagues , my Friends and even all my patients for their continuous help, encouragement and support.*

Ahmed Mowafy

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Endocrine scheme

These points should be discussed in any endocrinal disease:

1. Physiology.
2. Etiology.
3. Clinical picture.
4. Differential diagnosis.
5. Investigation.
6. Treatment.

1. Physiology :

4 items

- a. Hormone.
- b. Gland.
- c. **Function of the hormone.**
- d. Regulation of this hormone.

2. Etiology :

a. Hyper :



- i. Tumor : **adenoma**. (benign > malignant)
- ii. Hyperplasia.
- iii. Paramalignant syndrome.

b. Hypo :



- i. Surgery.
- ii. Irradiation.
- iii. Tuberculosis, sarcoidosis, hemochromatosis. ♪ ♪

3. C / P :

- a. C / p of the cause : e.g. pressure manifestations , tumor
- b. C / p of the hormone :
 - i. Hyperfunction = function of the hormone.
 - ii. Hypofunction = opposite the function of the hormone.

N. B. Neurological manifestations : depression & polyneuropathy → may occur in any endocrinal disease.

4. Differential diagnosis : Differs according to each hormone.

5. Investigation :

a. Inv. for the cause : e.g. Imaging for the gland : U/S , CT , MRI .

b. Assay of the hormone level :

i. In blood : ↑ in hyper , ↓ in hypo

- 2 - 3 times to avoid the diurnal variation.
- It's not an ideal method because the plasma level of all hormones varies through the day (because of pulsatile secretions).

ii. In urine :

1. hormone.
2. metabolite of the hormone.

c. Investigations of the function of hormone : *see function .*

d. Dynamic test : *The principle is :*

- If a hormone level is high → suppress it.
- If a hormone level is low → stimulate it.
- **Suppression test** → for Hyperfunction.
 - Normal : +ve (*suppression of the hormone*)
 - In this case (.....) : - ve (*no suppression*).
- **Stimulatory test** → for Hypofunction.
 - Normal : +ve (*stimulation of the hormone*)
 - In this case (.....) : - ve (*no stimulation*).

6. Treatment :

a. Hyper :

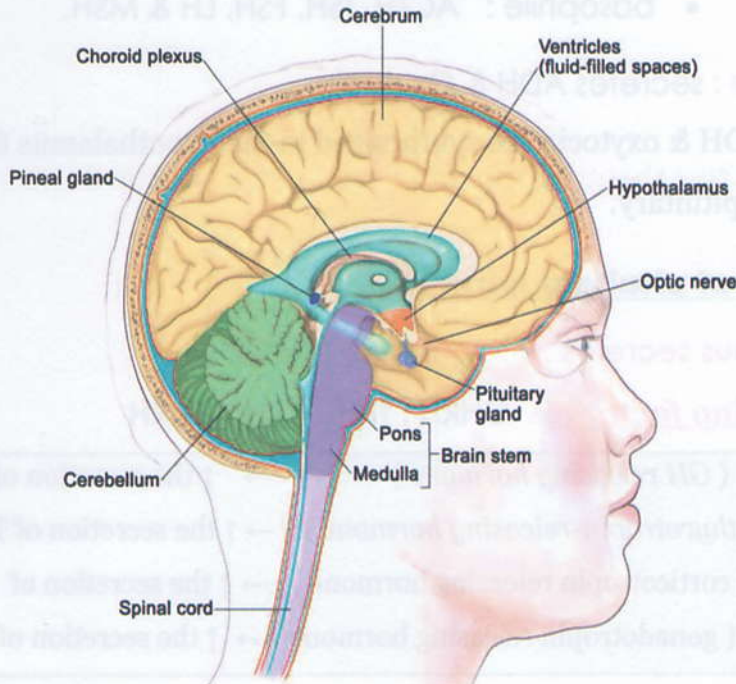
- i. Surgery.
- ii. Irradiation.
- iii. Medical antagonist.

b. Hypo :

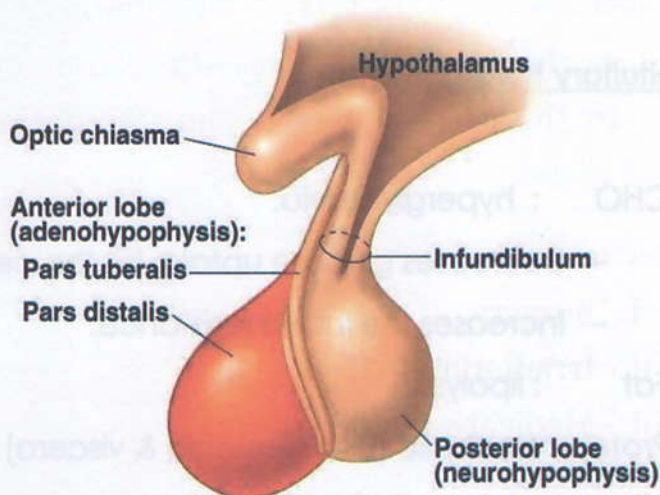
- i. Replacement therapy.
- ii. Treatment of the cause.

Pituitary gland

- Present in Sella turcica at the base of the skull.
- Weight 0.5 gm.



- It is divided into 2 lobes :
 - i. Anterior lobe.
 - ii. Posterior lobe.



- Anterior lobe → connected to the hypothalamus by vascular connection
- Posterior lobe → connected to the hypothalamus by neural connection.

▪ anterior lobe :

- **Chromophobes** : non functioning (non secreting).
- **Chromophils** :
 - acidophil : GH & prolactin.
 - basophile : ACTH, TSH, FSH, LH & MSH.

▪ **Posterior lobe** : secretes ADH & Oxytocin.

In fact, ADH & oxytocin are synthesized in the hypothalamus & stored in the posterior pituitary.

▪ Regulation of pituitary hormones :

i. hypothalamus secretes :

➤ **Releasing factors** : GHRH , TRH , CRH , GnRH

- GHRH (*GH releasing hormone*) → ↑ the secretion of GH.
- TRH (*thyrotropin-releasing hormone*) → ↑ the secretion of TSH & Prolactin ?
- CRH (*corticotropin releasing hormone*) → ↑ the secretion of ACTH
- GnRH (*gonadotropin releasing hormone*) → ↑ the secretion of LH , FSH

➤ **Release inhibiting factors** : ↓ secretion of pituitary hormones.

ii. **Secretion of hormones is also regulated by -ve feedback mechanism :**

e.g. $\uparrow T_3 \rightarrow \downarrow TSH$, $\uparrow \text{cortisol} \rightarrow \downarrow ACTH$.

▪ Function of the pituitary hormones :

- **GH** :

- CHO : hyperglycemia.
 - Decreases glucose uptake by the cells.
 - Increases the insulin resistance.
- Fat : lipolysis.
- Protein : anabolic (bone, muscle & viscera)
- Minerals : $\uparrow$ (Na, K, Ca & PO₄).

- **Prolactin** : milk secretion.

- FSH :

- ♀ → maturation of graffian follicle.
- ♂ → spermatogenesis.

- LH :

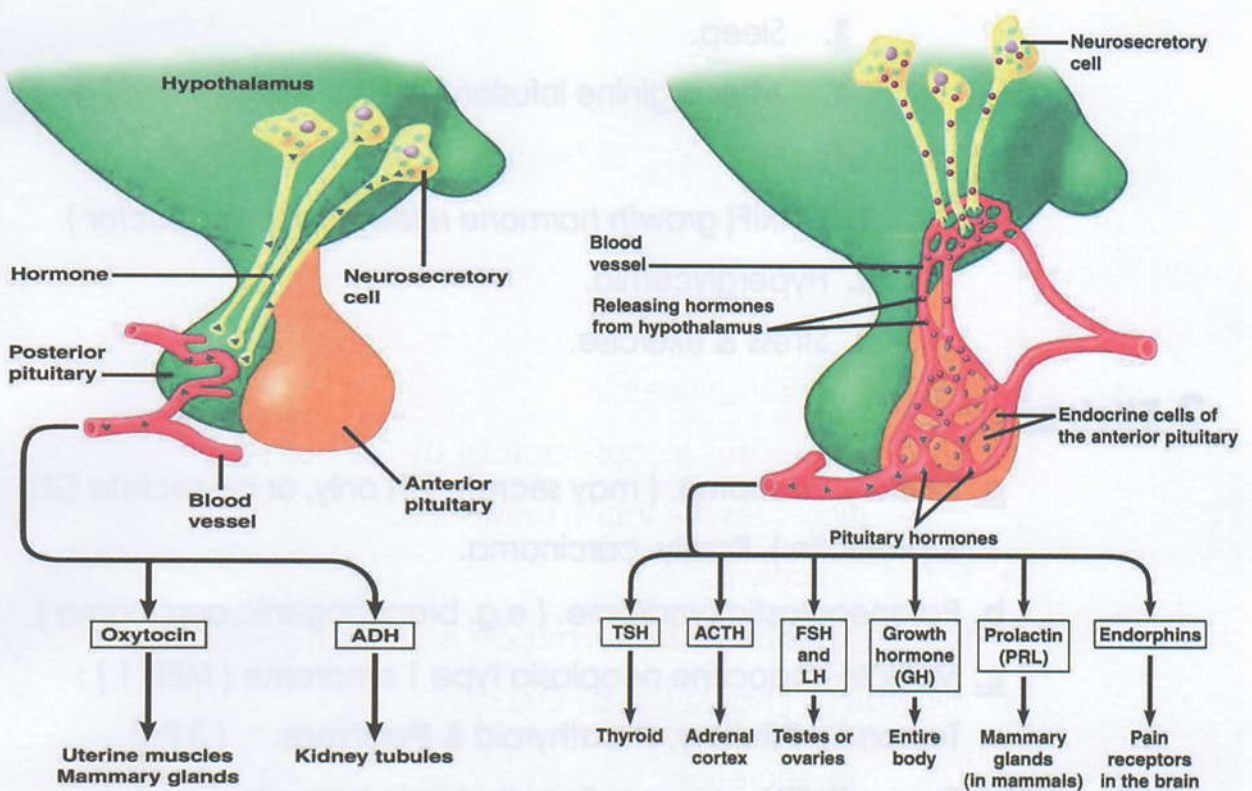
- ♀ → ovulation.
- ♂ → testosterone formation by the testis.

- ACTH :

- Secretion of suprarenal hormones :
 - cortisone +++
 - androgen ++
 - aldosterone + (under stress only)

- TSH : Secretion of thyroxin by thyroid gland.

- MSH : Skin pigmentation.



Acromegaly

Excessive secretion of GH in adults (after fusion of the epiphysis)

Physiology :

a. Hormone : Growth hormone (GH)

b. Gland : Pituitary gland (anterior lobe)

c. Function of the hormone :

i. **CHO** : hyperglycemia.

ii. **Fat** : lipolysis.

iii. **Protein** : anabolic (bone, muscle & viscera).

iv. **Minerals** : ↑ (Na, K, Ca & PO₄).

d. Regulation of this hormone :

i. ↑ GH :

1. GHRF. (growth hormone releasing factor)
2. Hypoglycemia.
3. Sleep.
4. After arginine infusion.

ii. ↓ GH :

1. GHRIF(growth hormone release inhibiting factor)
2. Hyperglycemia.
3. Stress & exercise.

2. Etiology :

a. Pituitary adenoma. (may secrete GH only, or co-secrete GH & prolactin). Rarely, carcinoma.

b. Paraneoplastic syndrome. (e.g. bronchogenic carcinoma)

c. Multiple endocrine neoplasia type 1 syndrome (MEN 1) :
Tumors in **P**ituitary, **P**arathyroid & **P**ancreas. (3 Ps)

d. Excess GHRH : rare e.g. hypothalamic hamartoma.

3. C / P :

a. C / p of the cause :

Pressure manifestations of pituitary adenoma : visual field defect.

b. C / p of the hormone :

- i. **CHO** : DM in 25 % of cases.
- ii. **Fat** : excess lipolysis → loss of sc fat , wrinkling of the skin.
- iii. **Protein** : excess growth of **bone, muscles, viscera.**

1. **bone :**

a. Skull : Periosteal new bone formation in the skull & mandible results in :

- i. Frontal **b**ossing, maxillary overgrowth, nasal **b**roadening.
- ii. **P**rominent supra-orbital ridges & mastoid processes.
- iii. **Prognathism** : prominent lower jaw with separated teeth.
- iv. **Hypertrophy of larynx & tongue** : hollow deep voice & sleep apnea.

These changes result in coarsening of facial features that are noticed when old patient pictures are seen.



b. Hands & feet :

- i. Spade hands & enlargement of feet.
- ii. Frequent change in rings & shoes size.
- iii. Hypertrophy of joint cartilage & osseous overgrowth result in carpal tunnel syndrome & osteoarthritis.

2. **Visceromegaly :**

- a. Hepatosplenomegaly.
- b. Cardiomegaly → congestive heart failure.

- c. Colonic polyps & increased risk of colonic cancer.
- d. Endothelial hyperplasia → hypertension.
- e. Hypertrophy of the skin, sweat & sebaceous glands resulting in moist greasy skin.

3. Muscle power :

a. ↑↑ early.

b. ↓↓ Late. (needless to say why ? ☺)

iv. Minerals :

- a. ↑ Na → hypertension.
- b. ↑ K → muscle weakness, arrhythmias.

v. Neurological manifestations :

- a. Depression.
- b. Carpal tunnel syndrome.
- c. Peripheral neuropathy.
- d. Spinal cord compression.
- e. Proximal myopathy.
- f. Pressure manifestations of the tumor in the skull.

Causes of carpal tunnel syndrome : Just remember

DR Ahmed Mowafy ☺

D : DM

R : Rheumatoid arthritis

A : Acromegaly

M : Myxedema & Musicians.

vi. Associated endocrinal manifestation :

- DM in 25 % of cases. (GH is an anti-insulin hormone).
- **Hyperprolactinemia due to :**
 - Co secretion from acidophils. (25% of pituitary adenomas)
 - Pituitary stalk compression → decrease of hypothalamic prolactin release inhibitory factor (PIF).
- Deficiency of other anterior pituitary hormones due to compression of the anterior pituitary.
- Hypogonadism if associated with Hyperprolactinemia or decreased pituitary gonadotropins.
- Rarely, diabetes insipidus : due to compression of the posterior pituitary.

4. Investigation :

a. Investigations for the cause : Imaging for the gland : Skull X-ray, CT & **MRI**

b. Assay of the hormone level :

1. **Fasting GH** : ↑ [normal < 5 n.gm/ml]
2. ↑ **Insulin growth factor-1** (IGF-1 , somatomedin)
3. Hyperprolactinemia & suppression of other anterior pituitary hormones may occur.

*GH is difficult to measure because of its pulsatile secretions So , **insulin growth factor** (IGF-1) produced by the liver in response to GH is measured instead.*

c. Investigations of the function of the hormone :

i. **Blood** : ↑ glucose, Na, K, Ca & P.

ii. **X-ray** :

1. **Skull** :

- Thick cortex.
- Widening of sella turcica & nasal sinuses.
- Prominent supraorbital ridges & occipital protuberance.
- Prognathism with wide separation of teeth.

What laboratory tests should be performed initially?

IGF-1 confirmed by glucose suppression test.

2. **Hand** : tufting of the terminal phalanges (mushroom shape)

d. Suppression test : **glucose IV** (oral glucose tolerance test)

1. Normally → +ve (↓ GH level)
2. In acromegaly → -ve (no suppression).

After overnight fasting, 50 - 100 g of oral glucose causes suppression of GH over the subsequent 30 - 90 minutes to < 2 ng/ml in normal persons but remain above 2 ng/ml in acromegalic patients.

e. Others :

Echocardiography and colonoscopy should be performed to evaluate for cardiomegaly and colon polyps.

5. Treatment :

- a. Surgery :** hypophysectomy. (The preferred initial treatment)
- b. Radiotherapy :** if GH is still elevated after surgery or if complete excision of the tumor is not possible or in a case of recurrence.
- c. Medical treatment :**
 - ✗ SC Somatostatin analogues [GHRIF] : e.g.
 - ✓ Octreotide.
 - ✓ Lanreotide, Pasireotide : newer somatostatin analogues.
 - ✗ GH receptor antagonists : Pegvisomant.
 - ✗ Dopamine agonists : less effective than octreotide. A large dose is needed with increased incidence of side effects.
 - ✗ Symptomatic treatment : DM , Hypertension.

Gigantism

Definition : ↑↑ GH secretion before fusion of epiphysis.

C/P :

1. Generalized overgrowth of skeleton & soft tissue.
2. Disproportionate gigantism. (span more than height).
3. Later on features of acromegaly develops.
4. Lastly decline stage usually occurs (pituitary hypofunction)

Differential diagnosis of tall stature:

1. Familial & racial : [the commonest]
2. Gigantism.
3. Excess androgen → tall children , short adult
4. 1ry hypogonadism : Disproportionate gigantism with feminine character.
5. Marfan & Klinefelter syndromes.

Hyperprolactinemia

1. Physiology :

- a. **Hormone** : Prolactin.
- b. **Gland** : Pituitary gland [*anterior lobe, prolactin acidophils*].
- c. **Function of the hormone** : milk secretion.
- d. **Regulation of this hormone** :
 - i. ↑ prolactin : Recently it's thought that TRH (thyrotropin releasing hormone) is a prolactin releasing hormone.
 - ii. ↓ prolactin : prolactin release inhibiting hormone (PRIH , dopamine)

2. Etiology :

a. Physiological :

- o Pregnancy, Breast feeding, Breast stimulation.
- o Sleep, Stress, Suckling.

b. Drugs : Antidopaminergic drugs MCQ

- i. Antipsychotics : Phenothiazine (chlorpromazine), Haloperidol.
- ii. Antidepressant :
 - o Tricyclic Antidepressants : Amitriptyline.
 - o Selective Serotonin Reuptake Inhibitors (SSRI) : Paroxetine.
- iii. Antiemetic : Metoclopramide, Domperidone.
- iv. Antihypertensive : α-Methyl-dopa, reserpine, verapamil.
- v. Others : Morphine, Estrogen, Cimetidine.

c. Pathological :

- i. Pituitary : Prolactinoma (*prolactin secreting pituitary adenoma*),
Mixed pituitary adenomas : GH/Prolactin
- ii. Hypothalamic tumors.
- iii. Thyroid : 1ry hypothyroidism → ↑ TRH → ↑ prolactin.

- iv. Renal : CRF $\rightarrow$ $\downarrow$ prolactin clearance.
- v. Liver cirrhosis : $\rightarrow$ $\downarrow$ metabolism.

3. Clinical picture :

a. C / p of the cause : visual disturbance due to pituitary adenoma.

b. C / p of the hormone :

i. In female :

1. **Galactorrhea** : persistent milk production in a ♀ who is not postpartum.
2. Amenorrhea.
3. Osteoporosis (due to estrogen deficiency).

ii. In male :

1. Gynecomastia.
2. Impotence & $\downarrow$ libido.
3. Infertility.

Hyperprolactinemia suppresses GnRH causing decreased FSH & LH

4. Investigation :

a. Investigations for the cause : Pituitary imaging : X ray , CT , MRI.

b. Assay of prolactin level :

Prolactin > 250 ng/ml suggest probable pituitary adenoma. [n < 20 ng/ml]

5. Treatment :

a. Dopamine agonist :

- i. Bromocriptine : 2.5 mg orally, $\uparrow$ gradually to 10 mg/d.
- ii. Cabergoline : drug of choice : less side effects.
 - o Effect : Lower prolactin level with reduction of the tumor size in about 70-90%
 - o S/E : nausea, vomiting, abdominal pain, hallucinations.

b. Surgery: for macroadenoma not responsive to medical treatment.

c. Irradiation : proton or α particles.

d. Treatment of the cause : e.g. myxoedema.

Pituitary tumors

Tumor Type	Secretory Product(s)	Relative Frequency (%)
Prolactinoma (<i>Lactotroph Adenoma</i>)	Prolactin	50
Somatotroph Adenoma	Growth Hormone	10
Corticotroph Adenoma	ACTH	5
Thyrotroph Adenoma	TSH	1
Non secreting Adenoma	-----	34

Nelson's syndrome :

Big pituitary adenoma with very high ACTH & hyperpigmentation after bilateral adrenalectomy in a case of pituitary Cushing.

Pituitary apoplexy : It is an endocrinology emergency

Sudden enlargement of the pituitary by hemorrhage into the tumor , causing combination of pressure manifestations (e.g. visual defect) & panhypopituitarism.

Try to learn something about everything and every thing about something.

Thomas Henry Huxley

Panhypopituitarism in adults

(Loss of anterior pituitary function)

1. Etiology :

a. Destruction of pituitary gland by :

- i. Surgery .
- ii. Irradiation.
- iii. Tuberculosis, sarcoidosis, hemochromatosis. ♪♪

b. **Sheehan syndrome** : pituitary infarction after sever postpartum hemorrhage

c. **Pituitary apoplexy** : Hemorrhage in pituitary tumor.

d. Genetic : Isolated GH or GnRH deficiency.

e. Autoimmune.

2. C / P :

a. C / p of the cause : Surgery , Sever post-partum hemorrhage.

b. C / p of the hormones :

According to the frequency of appearance : 2 G → **GH & Gondotrophins (FSH , LH)**
are lost early then **TSH** then **ACTH** deficiency.

i. Gonadal deficiency :

1. ♀ : amenorrhea, ↓ libido, infertility, loss of pubic & axillary hair.
2. ♂ : impotence, ↓ libido, infertility, loss of pubic & axillary hair.

ii. GH deficiency :

a) Adult : Fasting hypoglycemia, osteoporosis & fine wrinkles.

b) In Children :

- GH deficiency only : short stature with proportionate dwarfism.
- GH with FSH & LH deficiency : dwarfism with infantile proportions (upper > lower segment & span shorter than height.

- iii. TSH deficiency : result in 2ry hypothyroidism. In contrast to 1ry hypothyroidism hypercholesterolemia is rare. Skin is thin with wrinkling. Also, no menorrhagia in 2ry hypothyroidism. **MCQ**
- iv. ACTH deficiency : Results in 2ry adrenal insufficiency, it simulates Addison's disease but :
 - 1. No pigmentation (absent ACTH)
 - 2. No marked hypotension , due to normal aldosterone.
- v. Prolactin : Low with failure of lactation in Sheehan syndrome. It may be high in lesions causing pituitary stalk compression.
- vi. Coma : due to
 - 1. Hypoglycemic coma due to ↓ GH & cortisone.
 - 2. Myxedema coma.
 - 3. Pressure in cases of pituitary tumors.

NB : *If the patient has associated DI : the problem is at the hypothalamus.*

3. Differential diagnosis :

- a. From 1ry Addison's disease & 1ry hypothyroidism : see later
- b. From anorexia nervosa :
 - i. Normal hair & breast. ii. Aggressive attitude.
 - iii. Normal cortisol & High GH due to hypoglycemia.

4. Investigation :

- a. Investigations for the cause : Pituitary imaging : X-ray , CT & **MRI**
- b. Assay of the hormones level :
 - 1. ↓ GH [n : 1 – 5 n.gm/ml] & ↓ IGF-1.
 - 2. ↓ FSH, ↓ LH & ↓ sex hormones.
 - 3. ↓ TSH, ↓ T3 & ↓ T4.
 - 4. ↓ ACTH & ↓ cortisol.
 - 5. Prolactin : Low or high (see above)

C. Investigations of the function of the hormone : e.g.

1. Hypoglycemia.
2. Hyponatremia.

d. Stimulatory test : *insulin tolerance test*

- It is a gold standard for diagnosis of GH deficiency.
- After overnight fasting, regular insulin (0.1 U/Kg) is given :
 1. Normal : +ve ($\uparrow$ GH > 7 ng/mL)
 2. In pan-hypopituitarism : -ve (no stimulation).

5. Treatment :

a. Treatment of the cause.

b. Replacement therapy : *Multiple hormones must be replaced.*

i. Hydrocortisone : 30 mg/ d. (20 mg a.m. & 10 mg p.m.)

ii. Gonadotrophin deficiency :

If fertility is not a problem :

- ✎ In males : testosterone.
- ✎ In females : estrogen / progesterone.

If fertility is a problem : (both males & females)

- ✎ LH : Human chorionic gonadotropin (hCG).
- ✎ FSH : human menopausal gonadotropin.
- ✎ GnRH : may be occasionally used.

iii. TSH deficiency : Oral Levo-thyroxine, **should be started after steroid replacement, to avoid acute adrenal failure.**

iv. ADH deficiency : desmopressin (intranasal, SC, oral)

v. Recently :

1. Purified pituitary hormones.
2. Hypothalamic releasing factors.

Differential diagnosis of short stature

1. **Familial & constitutional** : the commonest.

2. **Endocrinal** :

- a. ↓ GH : Levi-lorain , Frolich's, Lurance Moon Biedle *
- b. ↓ T4 : cretinism & juvenile myxedema.
- c. ↑ sex hormones : precocious puberty.
- d. ↑ cortisol : Cushing or excess cortisone therapy.
- e. Type 1 DM.

* *Levi-Lorain syndrome* : proportionate dwarfism , hypogonadism , normal mentality.

* *Frolich's syndrome* : trunk obesity , hypogonadism , polyphagia & mental retardation.

* *Lurance moon biedle* : like Frolich's + Skull deformity & retinitis pigmentosa.

3. **Chronic sever illness during childhood** :

- a. **CVS** : sever rheumatic fever, congenital heart diseases.
- b. **Chest** : polycystic lung disease , TB.
- c. **GIT** : malabsorption syndrome & malnutrition.
- d. **Kidney** : chronic nephritis.

4. **Skeletal causes** :

a. **Congenital** :

- i. Achondroplasia : short limbs with normal trunk.
- ii. Osteochondrodystrophy : both limbs & trunk are short & deformed.

b. **Acquired** :

- i. Rickets.
- ii. Pott's disease of spine.
- iii. Paget's disease of bone.

5. **Genetic causes** :

- a. Mongolism [Down's syndrome] trisomy 21.
- b. Turner's syndrome [45+ XO].
- c. Noonan's syndrome.

Diabetes insipidus

Deficiency of ADH

1. Physiology :

a. Hormone : ADH (antidiuretic hormone , vasopressin).

b. Gland : Pituitary gland (posterior lobe).

ADH is synthesized in hypothalamus & then transported along axons & stored in the posterior Pituitary.

c. Function of the hormone :

i. ↑↑ water reabsorption by collecting tubules.

ii. Large dose → vasoconstriction of blood vessels.

d. Regulation of this hormone :

i. ↑↑ ADH by :

1. ↑ osmolality.

2. Hypovolemia & hypotension.

3. Drugs : nicotine , barbiturates.

ii. ↓↓ ADH by : ↓ osmolality, Hypertension & Cold weather.

2. Etiology :

a. Central DI : (damage of hypothalmo-hypophyseal axis)

i. Idiopathic : Hereditary (autosomal dominant)

ii. Injury : after hypophysectomy.

iii. Infection : T.B.

iv. Infiltration : sarcoidosis

v. Infarction : Sheehan syndrome.

vi. pituitary tumor.

vii. **Pregnancy** : deficiency of ADH can result from increased metabolism by a placental enzyme (vasopressinase enzyme). It resolves within a few weeks after delivery.

b. Familial DI (*Wolfram syndrome* , **DIDMOAD**)

hereditary condition in which there is a defect in osmo-receptors

- i. **D**iabetes **I**nsipidus.
- ii. **D**iabetes **M**ellitus.
- iii. **O**ptic atrophy.
- iv. **D**eafness.

Osmoreceptors are present in
anterior hypothalamus.

c. Nephrogenic DI (Renal tubules not responding to ADH)

- i. Hereditary (X-linked recessive so, *males are predominantly affected* ☹)
- ii. **Acquired** : **MCQ**
 - 1. Chronic renal failure.
 - 2. Kidney amyloidosis.
 - 3. Polycystic kidney & Pyelonephritis.
 - 4. Hypercalcemia & Hypokalemia.
 - 5. Drugs : Lithium , Cholchicine, Demeclocycline.

3. C / P :

a. C / p of the cause : e.g. history of hypophysectomy.

b. C / p of the hormone :

- i. **Polyuria** (up to 20 L/day) & polydipsia.
- ii. Severe dehydration → weakness , weight loss & fever.
- iii. Hypovitaminosis : of water soluble vitamins.
- iv. Complications : shock & death.

4. Differential diagnosis : DD of polyuria. [*discussed later*]

5. Investigation :

a. Investigations for the cause : Pituitary Imaging : X-ray , CT & MRI

b. Assay of the hormone level : ↓

c. Investigations for the function of ADH :i. Urine analysis :

1. Polyuria with low Specific gravity.
2. No pathological constituents.
3. After fluid deprivation : Polyuria persists.

ii. Plasma osmolality : ↑ due to loss of free water.d. Stimulation tests :i. Test the hypothalamus : **nicotine** test (1-3 mg nicotine)

1. normal : oliguria due to stimulation of ADH.
2. central DI : -ve (no stimulation)

ii. Test osmo-receptors : IV hypertonic saline (NaCl 2.5 %) .

1. normal : oliguria.
2. osmo-receptors defects : -ve (no oliguria)

iii. Test kidney (vasopressin test) :

to differentiate between central DI & nephrogenic DI

1. in **C**entral DI : oliguria (**C**oncentrated urine)
2. in **N**ephrogenic DI : **No** change.

6. Treatment :

a. Replacement therapy : synthetic ADH (*Desmopressine*) 20 µg/d intra nasal

b. Diet : ↓ Na , ↑ vitamins.

c. Drugs : 3 C ☺ MCQ

- ✎ Cholpropamide : for central DI.
- ✎ Carbamazepine : in nephrogenic DI.
- ✎ Thiazide may be used in nephrogenic DI.
- ✎ Amloride (potassium-sparing diuretic) : is the drug of choice in lithium toxicity induced DI.

Differential diagnosis of polyuria

Urine output > 3L/d in adult

1. Physiological :

- Winter months.
- Excess coffee or tea.
- Diuretics.

2. Psychological : Hysterical polydipsia.

	<i>DI</i>	<i>Hysterical polydipsia</i>
C/P :	Polyuria then polydipsia	Polydipsia then polyuria
Fluid deprivation test :	Polyuria persists	No polyuria
Osmolality	↑↑	↓↓

3. Pathological :

a. Endocrinal :

- i. DI : with its causes.
- ii. DM
- iii. Adrenal : Conn's (hypokalemia), Addison's.
- iv. Thyroid : thyrotoxicosis (↑ metabolic water)
- v. Parathyroid : hyperparathyroidism.

b. Renal :

- i. Nephrogenic DI.
- ii. Chronic renal failure.
- iii. Diuretic phase of acute renal failure.

c. After any attack :

- i. Migraine
- ii. Epilepsy
- iii. Bronchial asthma
- iv. Also after the internal medicine exam. ☺

Syndrome of inappropriate ADH secretion (SIADH)

It means an excessive release of ADH

1. Physiology : Refer to diabetes insipidus.

2. Etiology :

- a. Tumors release ADH : Oat cell carcinoma & lymphoma.
- b. Pulmonary lesion : Legionella pneumonia, TB.
- c. CNS : meningitis, encephalitis & head injuries.
- d. Drugs : **chol**lorpropamide , **carb**amazepine , **cyclo**phosphamide.

3. C / P :

- Increased ADH causes water retention → **dilutional hyponatremia**
(weight gain , weakness , **c**onfusion, **c**onvulsions & **c**oma)
- No edema because of natriuresis.

4. Investigation :

1. ↓ **Na** (< 130 mEq /L)
2. ↓ serum osmolality (< 270 mosmol/kg) .
3. ↑ **urine Na concentration** (> 20 mEq/L).

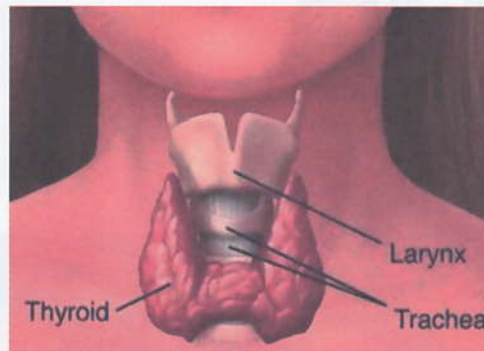
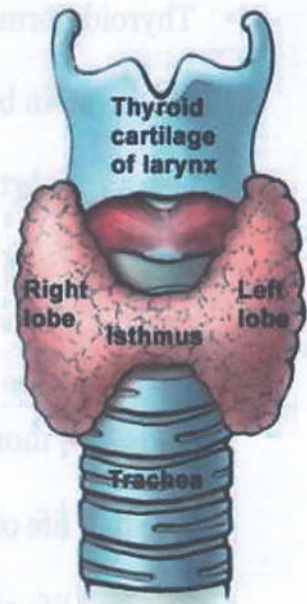
5. Treatment :

- a. Fluid restriction → 0.8 -1 L / day.
- b. **Demeclocycline:**
 - i. 600 -1200 mg /day → inhibit the action of ADH.
 - ii. Given to patient unresponsive to fluid restriction.
- c. For sever hyponatremia : hypertonic saline (5%) IV slowly.

Thyroid gland

Anatomy :

- The thyroid gland is an H shaped or butterfly shaped gland located in the lower neck in front of the trachea and between the carotid arteries.
- It is formed of 2 lobes connected to each other by an isthmus. Its normal weight is about 10 – 25 gm.
- It's attached to the thyroid cartilage & to the upper end of trachea so , it moves with swallowing.

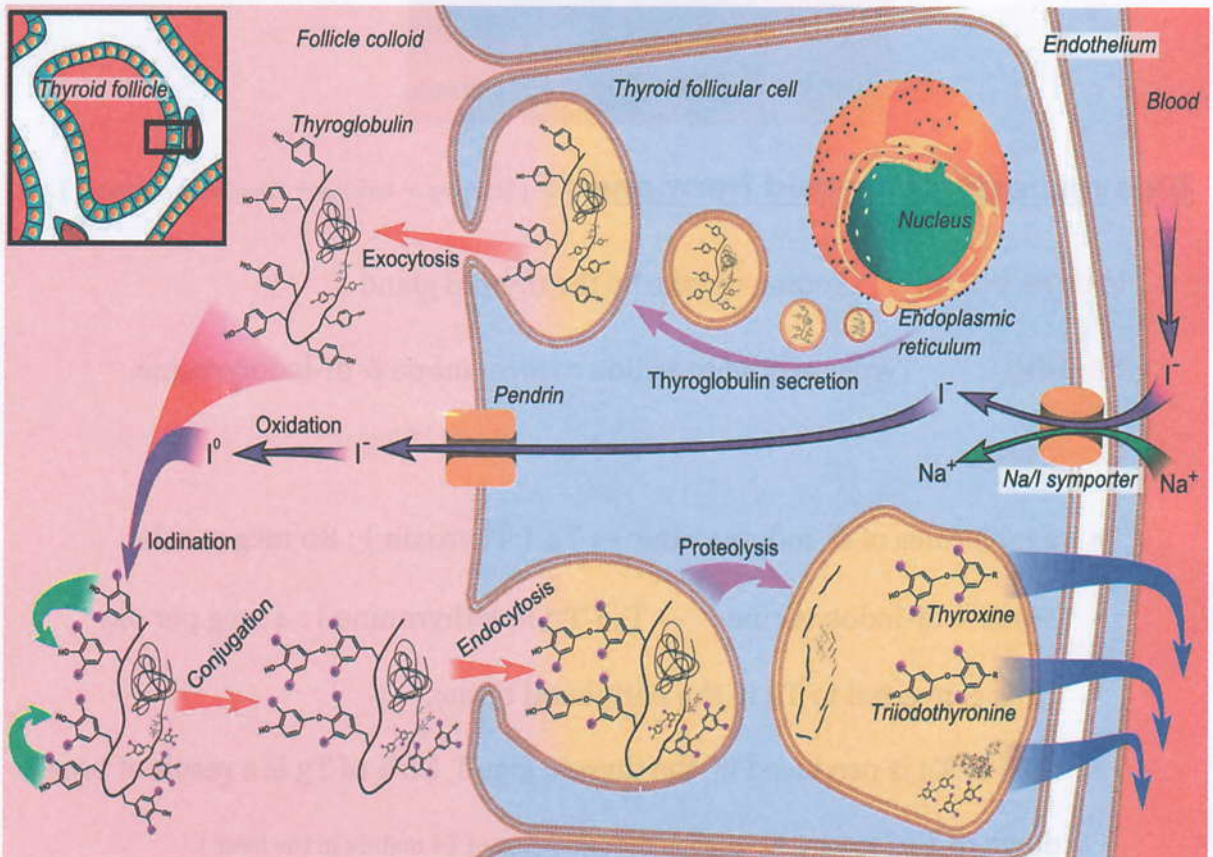


Biosynthesis of thyroid hormones : (Trapping → Binding → Coupling → Release) ☺

- 1. Iodine trapping :** Iodine uptake by the thyroid gland .
- 2. Binding :** Tyrosine bind to iodine to form mono & di-iodotyrosine.
- 3. Coupling :**
 - 2 molecules of di-iodotyrosine → T₄ (Thyroxin) : 80 mcg per day
 - Mono + di-iodotyrosine → T₃ (Tri iodothyronine) : 4 mcg per day
 - T₄ is converted to T₃ in the peripheral tissue.
 - 20% of T₃ is produced by the thyroid gland, 80% of T₃ is a result of break down of T₄ (monodeiodination of the outer ring of T₄ mainly in the liver).

4. Release :

- T₃ & T₄ release under the control of TSH.
- Thyroid hormones circulate in 2 forms :
 - ✓ Protein bound, mainly *thyroxine binding globulin* (TBG) : > 99 %
 - ✓ Free part (active part) :
 - 0.03 % of total serum T₄ is free.
 - 0.3 % of total serum T₃ is free
- T₃ is 3 - 8 more potent than T₄ and acts more rapidly.
- The half life of T₃ is ~ 24 hours.
- The half life of T₄ is about one week.



Thyroid diseases

Causes of hyperthyroidism (thyrotoxicosis) :

1. **Toxic diffuse goiter** : The most common cause of hyperthyroidism.
(**Grave's disease** in USA, Basedow's disease in Europe).
 2. **Toxic multinodular goiter.**
 3. **Toxic solitary adenoma.**
 4. Excess production of TSH by pituitary tumor (very rare).
 5. Hashimoto's thyroiditis with transient hyperthyroid phase.
 6. Extrathyroid source of hormone :
 - a. Thyrotoxicosis factitia : exogenous intake of thyroxin.
 - b. Ectopic thyroid tissue e.g. struma ovarii .
 7. Iatrogenic : amiodarone.
-

Classification of hypothyroidism :

➤ According to the age of onset :

1. Cretinism : during infancy.
2. Juvenile myxedema : before puberty.
3. Myxedema : after puberty.

➤ According to the site of the cause :

1. 1ry hypothyroidism : cause in the thyroid gland.
2. 2ry hypothyroidism : cause in the pituitary gland.
3. 3ry hypothyroidism : cause in the hypothalamus.

1ry thyrotoxicosis (Graves' disease)

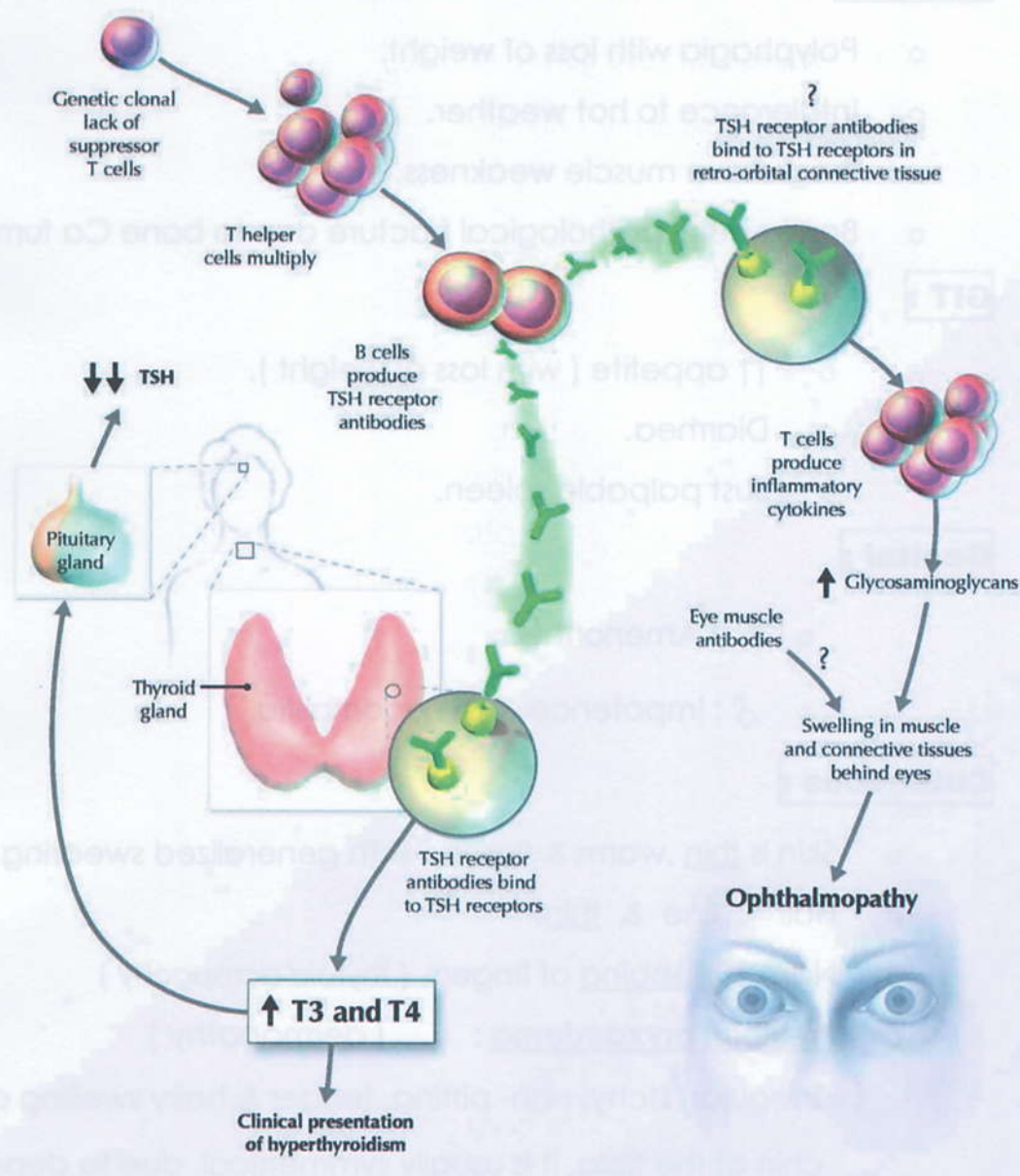
- It is the most common cause of hyperthyroidism.
- Autoimmune disorder consists of :
 - Hyperthyroidism plus one or more of the following triad :
 - Painless diffuse goiter (90 %)
 - Ophthalmopathy (60 %)
 - Dermopathy. (2 %)

1. Physiology :

- a. Hormone : T3 (triiodothyronine) & T4 (thyroxine)
- b. Gland : Thyroid gland.
- c. Function of the hormone : *Hormone of metabolism*
 - i. Stimulate physical , mental & sexual growth.
 - ii. ↑ energy production & O₂ consumption.
 - iii. ↑ glucose absorption & uptake by cells.
 - iv. ↓ cholesterol & prolactin levels.
 - v. ↑ the respiratory & heart rate.
 - vi. Stimulation of erythropoiesis (↑ RBCs).
 - vii. ↑ the tissue responsiveness to catecholamine.
 - viii. Hepatic conversion of carotene to vitamin A .
- d. Regulation of this hormone :
 - i. TSH.
 - ii. TRH.

2. Etiology :

- **Autoimmune** disorder characterized by a variety of circulating antibodies(*Thyroid stimulating immunoglobulin* - TSI) that bind to and activate the thyroid TSH receptors.
- May be associated with other autoimmune disorders e.g. **autoimmune polyglandular syndrome II** (see later)



3. Clinical picture : (♀ 30 – 40 years).

a. C / p of the cause :

Association of autoimmune diseases : Polyglandular autoimmune syndrome II (Type1 DM, Adrenal failure & Grave's disease).

b. C / p of the hormone :

General :

- Polyphagia with loss of **w**eight.
- Intolerance to hot **w**eather.
- Progressive muscle **w**eakness.
- Bone : pain, pathological fracture due to bone Ca turnover.

GIT :

- ↑↑ appetite (with loss of weight).
- Diarrhea.
- Just palpable spleen.

Genital :

- ♀ : Amenorrhea.
- ♂ : Impotence & gynecomastia.

Cutaneous :

- Skin is thin ,warm & flushed with generalized sweating.
- Hair : fine & thin.
- Nails : clubbing of fingers. (*Thyroid acropachy*)
- Preitibial myxoedema : (*dermopathy*)

Irregular, Itchy, non- pitting, tender & hairy swelling over the chin of the tibia. It is usually symmetrical, due to deposition of mucopolysaccharide substance in the S.C. tissue.

CVS :(more common in older patients)**1- pulse :**

- **rate** : ↑ , the sleeping pulse rate is usually > 100 b/m .
- **rhythm** : may be irregular due to AF or extrasystole.
- **character** : water hammer pulse due to big pulse volume.
- **equality** : unequal on both sides → retro-sternal goiter.

Thyroid function tests are mandatory in any patient with atrial fibrillation

2- heart : Hyperdynamic circulation ⇒ volume overload ⇒ cardiac enlargement then heart failure.

3- Blood Pressure :

- systolic : ↑ (isolated systolic hypertension)
- diastolic : ↓ (thyroxin → VD)

*So, there is big pulse volume***CNS :**(more common in younger patients).**- Psychic : 4***mnemonic : naim*

- **Nervousness.**
- **Anxiety & agitation.**
- **Insomnia.**
- **Mental disturbance.**

- Organic : 4

- Fine tremors in tongue & hands.
- Polyneuropathy.
- Myopathy.
- Myasthenia.

It's important to note that elderly patients with hyperthyroidism may be apathic rather than nervous (**apathetic thyrotoxicosis**).

Eye :**1. Exophthalmos :**

- Bilateral , but may start unilateral.
- May occur even before the appearance of thyrotoxicosis.
- AE : oversecretion of autoantibody called **exophthalmos producing substance** (EPS) $\Rightarrow$ lymphocytic infiltration of retrobulbar tissue & extrinsic muscles.
- Orbital pain & photophobia may occur.
- Blindness may occur secondary to corneal ulcers or optic nerve compression.

2. certain eye signs : (DR must be very simple)

- a. **Dalrymple's sign** (Lid retraction) : rim of sclera is seen between the cornea & upper lid.
- b. **Rosenbach's sign** : fine tremors of eyelids on slight closure of eye.
- c. **Moebius' sign** : lack of convergence due to weak medial recti muscles.
- d. **Von-Grave's sign** : lid lag on looking down.
- e. **Stellwag's sign** : infrequent blinking.

N.B: Ocular manifestations can be divided into 2 types :

- ✓ **Infiltrative ophthalmopathy** (mechanical , due to accumulation of autoantibodies) : specific to Grave's disease
 - Exophthalmos
 - Mobius sign
- ✓ **Non- Infiltrative ophthalmopathy** (due to $\uparrow$ thyroxin) :
e.g. lid lag, lid retraction , stellwag & Rosenbach's sign $\rightarrow$ occur with any thyrotoxicosis (not specific to Grave's disease).

Gland :

- a. Inspection : mild to moderate enlargement of the gland.
- b. Palpation : - consistency : fleshy or firm. – surface : smooth.
- c. Percussion : dullness over manubrium-sterni in retro-sternal extension.
- d. Auscultation : systolic bruit may be heard due to high vascularity.

Thyrotoxic crisis (thyroid storm) :

- An extreme form of thyrotoxicosis with a mortality of 10 %.
- It's rare, life threatening endocrinal emergency.
- Precipitating factors :
 - Surgery. - Acute illness : MI, stroke, infection.
 - Parturition - Discontinuation of anti-thyroid drugs
- **C/P** : sever manifestations of thyrotoxicosis that include :
 - a) General : fever with temperature $> 41^{\circ}\text{C}$, marked weakness
 - b) C.V.S. : sever tachycardia, hypotension, acute HF & AF.
 - c) C.N.S. : tremors, marked irritability, confusion & coma.
 - d) Diarrhea, abdominal pain, hepatomegaly with mild jaundice.
- **Treatment** : see later

Differential diagnosis :

- a. Neurosis : → cold hand & normal sleeping pulse.
- b. ↑appetite with loss of weight: DM , parasitic infection.
- c. Hyperdynamic circulation.
- d. Muscle diseases : myopathies, myasthenia gravis.
- e. **Difference between 1ry & 2ry thyrotoxicosis**

	1 st thyrotoxicosis	2 nd thyrotoxicosis
- Other name :	Grave's disease.	toxic multi nodular goiter.
- Cause :	Auto-immune.	On top of nodular goiter.
- Age of onset :	30 – 50 year.	50 year.
- Thyroid gland :	Diffusely enlarged.	Nodular.
- CVS :	Mild.	Sever.
- CNS :	Sever.	Mild.
- Exophthalmos :	Present.	Absent.
- TTT :	Usually medical.	Usually surgical.

monosymptomatic cases : when one of the manifestations of thyrotoxicosis predominates
e.g. thyrocardia : cardiac symptoms only (AF) .

Investigation : (Thyroid function tests)

1. Investigations for the cause :

1. TSH level : [n = 0.5 – 5 μ U/L]

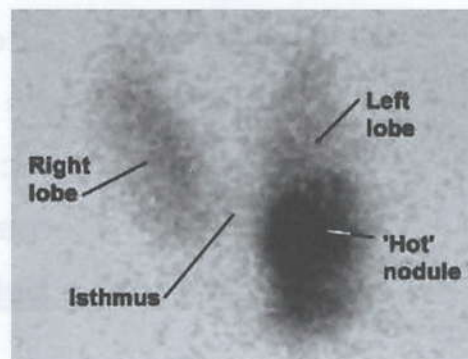
- It's the **most sensitive** test of thyroid function.
- $\downarrow\downarrow$ in most cases of thyrotoxicosis by –ve feed back mechanism.
- $\uparrow\uparrow$ only in **TSH producing pituitary tumor** : very rare.

2. Imaging for the gland :

a) Thyroid scan : (Radioactive nuclear medicine studies)

Radioactive material is injected into a vein or swallowed by mouth and the thyroid gland takes up this material :

- Hot nodule** : this tissue is rarely malignant.
- Cold nodule** : 10 to 15% of these tissues are malignant.



- b) **U/S** : indicated especially in cold solitary thyroid nodule
- Cystic → benign.
 - Solid : malignant → do needle aspiration biopsy.

So, everyone likes her to be hot & cystic, not cold & solid



- c) Fine Needle Biopsy (FNB) : a very small needle is introduced into the nodule and cells are aspirated for study.

3. Thyroid receptor antibodies : thyroid stimulating immunoglobulin (TSI) can be detected in Grave's disease.

The term LATS (long acting thyroid stimulator) referring to this antibody is no longer used.

II. Assay of the hormone level : 6

- a) Total T3 ↑↑ : [n : 70 – 170 ngm%] → not accurate.
- b) Total T4 ↑↑ : [n : 5 – 12 μgm%] → not accurate.

T3 & T4 are over 95% protein bound to TBG (thyroxin binding globulin) so,....

- Increased TBG as in pregnancy → ↑↑ total T3 & T4 but free T3 & T4 are normal.
- Decreased TBG as in liver cirrhosis & nephrotic syndrome → ↓ total T3 , T4 but free T3 , T4 are normal.

- c) **Free T3** (n : 0.4 ng %)
- d) **Free T4** (n : 1.6 ng %) difficult to measure , we use free T4 index.
- e) **T3 resin uptake** : ↑ (n = 25% - 35%)

Radioactive T3 is added to the patient's serum it's fixed to the unoccupied binding sites of TBG → the remaining radioactive is then absorbed into a resin

- f) **Free thyroxin index** : ↑ (> 11.5) = T3 resin uptake x total T4.

III. Investigations for the function of the hormone :

- Blood :
 - ✓ ↓ cholesterol , ↑ Ca , ↑ Calcitonin in medullary carcinoma.
 - ✓ Lag sugar curve.
- Urine : Polyuria , ↑ glucose.

IV. Suppression test : material : **T3** .

- ✓ Normally → ↓ RAIU (radio active iodine uptake).
- ✓ In thyrotoxicosis → no effect.

WHAT IS YOUR DIAGNOSIS ? SHOW ME UR INTELLIGENCE 😊😊		
Thyroid hormones & TSH	RAI Uptake scan (RAIU)	Diagnosis
1- ↓TSH, ↑ free T3 & T4	↑	
2- ↓TSH, ↑ free T3 & T4	↓	
3- ↓TSH, ↓ free T3 & T4	↓	

Answers to diagnosis column in table can be found at the end of this subject.

Treatment :

I. Medical :

Indication :

- 1ry thyrotoxicosis (Grave's disease).
- 2ry cases : pre-medication before operation.
- Treatment of complications e.g. HF.
- Pregnancy.

Contraindications :

- Huge goiter.
- Retro-sternal goiter.
- Suspicion of malignancy.

Lines of medical treatment :

✎ β -blockers (propranolol)

- Provide rapid symptomatic control : tachycardia, tremors & heat intolerance.
- They also decrease peripheral conversion of T₄ to T₃.

✎ Anti-thyroid drugs :

- Methyl thiouracil : **200mg** t.d.s. then reduce after 4-6 w to **100 mg** t.d.s.
- Propyl thiouracil : **100mg** t.d.s. then reduce after 4-6 w to **50 mg** t.d.s.
- Carbimazol (Neomercazol) : **20 mg** t.d.s. then reduce after 4-6 w to **10 mg** t.d.s.

▪ Duration : 1 - 2 years. (until thyroid hormone stores become depleted)

▪ Mechanism :

- These drugs inhibit the formation of thyroid hormones.
- Propylthiouracil : blocks iodination and coupling of tyrosines. Also, it inhibits peripheral conversion of T₄ to T₃.

▪ Side effects :

- Agranulocytosis .
- Hypothyroidism → ↑ TSH → Goiter.
- Relapse : on sudden stoppage.
- Others : GIT upset, cholestatic jaundice.

II. Radio-active iodine :

Indication :

- Failure of medical treatment.
- Patient is unfit for surgery.
- Recurrence after thyroidectomy.
- Toxic adenoma.

Contraindications :

- During pregnancy, lactation & childhood.
- Huge goiter, retro-sternal goiter & progressive exophthalmos.

Side effects :

- Hypothyroidism.
- Bone marrow depression.
- Fetal anomalies, if taken in pregnancy.
- ↑ incidence of malignancy, so → not given in childhood.

Precautions :

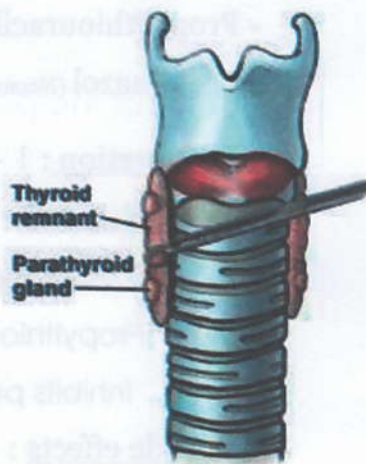
It's important to stop anti-thyroid drugs 4 days before & 4 days after radioactive iodine therapy as it prevents radioactive iodine uptake by the gland.

III. Surgical : (*sub-total thyroidectomy*)**Indications :**

- 2ry thyrotoxicosis.
- Failure of medical treatment.
- Huge or retro-sternal goiter.
- Suspicion of malignancy.
- Pregnant women not responding to drugs

Pre-operative preparations :

- Antithyroid drugs lead to euthyroid state.
- Lugol's iodine (5% iodine in 10% K iodide) : ↓ size & vascularity of the gland.

**Complications :**

- Laryngeal nerve palsy.
- Hypocalcaemia due to removal of parathyroid gland.
- Hypothyroidism.

IV. Treatment of complications :**➤ Ocular complications :**

- Protect eye by ointment, sun glasses, methyl cellulose.
- Prednisone → ↓↓ lymphocytic infiltration.
- Radiotherapy of the orbit.
- Orbital decompression.

➤ Heart failure :

- Bed rest, salt restriction, digitalis & diuretics.
- Persistence of AF → Digitalis or DC shock.

➤ **Preitibial myxoedema :**

- Remits spontaneously after months or years.
- Local Betamethasone cream (local steroid) relieves pruritis.

➤ **Treatment of Thyrotoxic crisis : 6**

1. **Propranolol** in full dose is started immediately for tachyarrhythmias
(160 mg/d orally, in 4 divided doses or 1 mg/4h IV)
 - It blocks the peripheral effects of thyroid hormone.
 - Also, it prevents the peripheral conversion of T4 to T3
 - The effects are dramatic and results may be seen within 10 min.
2. **Propylthiouracil** :
 - Dose : 600 loading dose then, 200 mg/6h. (orally, rectally or nasogastric tube).
 - It inhibits the synthesis of new thyroid hormone & prevents the peripheral conversion of T4 to T3.
 - Clinical effects may appear within 1 hour.
3. **Na iodide**: 1 gm over 24h IV → ↓↓ thyroxin release from thyroid gland.
4. **Hydrocortisone** : 100 mg/8h IV or IM, to correct the hypotension.

- *Thyrotoxic crisis → ↑↑ cortisol metabolism → relative adrenal insufficiency → refractory hypotension. Hydrocortisone correct this hypotension.*
- *Also, steroids prevent peripheral conversion of T4 → T3*

5. Treatment of precipitating factor : antibiotics for infections.
6. Symptomatic treatment :
 - Dehydration : IV fluid.
 - Hyperthermia : ice bags, paracetamol. Aspirin should be avoided as it decreases protein binding with subsequent increase in free T3 & T4
 - Later on restoration of euthyroid state may take up to 8 weeks

Thyrotoxicosis in pregnancy :

- Medical treatment : **p**ropylthiouracil.
- Carbimazole not preferred in pregnancy as it crosses the placenta & may cause congenital defects, including aplasia cutis of the neonate.
- Radioactive iodine : absolutely contraindicated as it is teratogenic & carcinogenic
- Surgery indicated in : appearance of side effects.
- Follow up: should be done to diagnose neonatal thyrotoxicosis because TSI can cross the placenta & stimulate fetal thyroid gland.

Answers to table : ☺

- 1- Primary hyperthyroidism.
- 2- Factitious hyperthyroidism or inflammation of the gland (Subacute thyroiditis).
- 3- Secondary or tertiary hypothyroidism.

Now, and after your journey with Hyperthyroidism,
REMEMBER that ..



Everyone likes her to be **Hot & Cystic** .. **NOT** .. **Cold & Solid**

I'm talking about thyroid nodule

- Hot nodule by thyroid scan & cystic by US : benign nodule.
- Cold nodule : may be malignant in about 10%

Myxedema

(Hypothyroidism in adult)

1. Physiology :

Refer to hyperthyroidism.

2. Etiology & types :

a. 1ry mxyedema : (5 I + H)

- i. **I**diopathic atrophy of the gland.
- ii. **I**atrogenic :
 1. post thyroidectomy.
 2. radioactive iodine.
 3. anti-thyroid drugs.
 4. lithium.
 5. amiodarone.
- iii. **I**nfections : viral infection (De Quervain's thyroiditis)
- iv. **I**odine deficiency.
- v. **I**nfiltration : tumor.
- vi. Hashimoto's thyroiditis :
 1. auto-immune disease. (thyroid antibodies : +ve).
 2. gland is replaced by lymphocytic infiltration.
 3. gland is firm, symmetrically enlarged & not tender.
 4. transient thyrotoxicosis may occur followed by hypothyroidism.

b. 2ry Myxedema : 2ry to pituitary failure e.g. tumor (↓ TSH).

c. 3ry myxedema: deficiency of TRH secreted from hypothalamus.

d. Peripheral resistance to thyroid hormone : very rare .

3. Clinical picture :

♀ > ♂ 30 – 50 years.



a. C / p of i cause : Surgery , Anti-thyroid drugs.

b. C / p of i hormone :

In hypothyroidism every thing slows down except the period !!

i. **General :**

1. Intolerance to cold.
2. Lethargy & fatigue.
3. Weight gain : due to decrease of metabolism, fluid retention, constipation.
4. Serous effusions (pleural , pericardial & ascites).

5. **Face :**

- a. Expressionless with puffy eye lids.
- b. Eyelids drop (decrease of adrenergic drive)
- c. Loss of outer 1/3 of eye brows.
- d. Large tongue.

ii. **GIT :**

1. **Slow** motility → constipation
2. **Slow** absorption → malabsorption syndrome.

iii. **Genital :**

1. ♀ → **Menorrhagia** in 1ry hypothyroidism
2. ♂ → Impotence & gynaecomastia.

iv. **Cutaneous :**

1. Dry, cold, pale & non sweaty skin.
2. Non pitting edema : due to intradermal accumulation of proteins, not interstitial edema fluid.
3. Yellowish discoloration due to carotinemia.
4. Hair loss.

v. **CVS :**

1. Hypercholesterolemia → ischemic heart disease.
2. Diastolic HTN due to ↓ thyroxin (thyroxin ⇌ VD)
3. Sinus bradycardia.
4. **Pericardial effusion.**

vi. **CNS :**

1. **Slow** intellectual & motor activity.
2. Depression, frank psychosis (*myxedema madness*)
3. Deposition of mucopolysaccharide in :
 - a. Tongue : **slow** speech.
 - b. Vocal cords : hoarseness of voice.
 - c. Flexor retinaculum : carpal tunnel syndrome.
 - d. Peripheral nerves : peripheral neuropathy.
 - e. Joints & muscles : **slow** relaxed reflexes.

vii. **Heamatological :**

1. Microcytic hypo-chromic anemia : iron deficiency anemia due to menorrhagia.
2. Macrocytic anemia : associated pernicious anemia.

viii. **Hypothyroid coma (Myxedema coma) :**

1. Untreated long standing hypothyroidism.
2. Precipitated by cold exposure & infections.
3. Manifested by : **5 H**
 - a. **H**ypothyroidism with loss of consciousness.
 - b. **H**ypothermia.
 - c. **H**ypoglycemia.
 - d. **H**ypoventilation.
 - e. **H**eat failure & **H**ypotension.

Although this condition is called Myxedema coma , frank coma is uncommon !!

ix. **Gland :**

- 1. Enlarged as → Hashimoto's thyroiditis.
- 2. Atrophy → 1ry idiopathic forms.
- 3. Scars of previous operations.

4. **Differential diagnosis :**

- a. Nephrotic syndrome.
- b. Depression.
- c. Other causes of hypothermia : cold weather, shock ..
- d. Difference between Primary & 2ry (pituitary) myxedema :

	Pituitary myxedema	thyroid myxedema
1. Clinical picture :		
o Skin	Depigmented, thin with wrinkling	Coarse, thick
o Macroglossia	No	Yes
o Menorrhagia	No	Yes
2. Investigation :		
a- TSH :	- Low	- High
b- FSH, LH, ACTH :	- Low	- Normal
c- Hypercholesterolemia	- Rare	- Common

MCQ

5. **Investigation :**

a. **Investigations for the cause :**

- i. **TSH :** [the **most sensitive** test for 1ry thyroid disease]
↑↑ in thyroid myxedema , ↓↓ in pituitary myxedema.
- ii. Thyroid antibodies.

b. **Assay of the hormones level :**

- 1. Serum hormones :
 - a. TSH : ↑↑ in 1ry type. [test of choice]
 - b. T4 & T3 : ↓↓

It is important to note that normal T4 not exclude hypothyroidism

- 2. Radio-active iodine uptake : ↓

c. Investigations of the hypofunction of thyroid hormone :i. Blood :

1. CBC : anemia
2. Blood glucose → flat sugar curve.
3. ↑ cholesterol & Prolactin.
4. ↑ CPK (creatinine phospho-kinase).
5. ↑ LDH (lactate dehydrogenase).

DD of low voltage ECG :

- Hypothyroidism.
- Pericardial effusion.
- Obesity.

ii. ECG findings : sinus bradycardia , **low voltage**.

iii. BMR : low.

6. Treatment :a. Replacement therapy : life long

- L-thyroxin : start small dose 0.05 mg/d & gradually up to maintenance dose (0.2 – 0.3 mg/day).
- The dose is increased very gradually to avoid precipitation of angina & HF.

b. Treatment of myxedema coma :

6

a. Hypothyroidism :

Large doses of T4 200 micro g IV & maintenance 50 micro g/d IV or
T3 : 40 micro g IV & maintenance 10 microgram/d IV.

b. Hypothermia : rewarming slowly to avoid arrhythmias.

c. Hypoglycemia : glucose IV.

d. Hypoventilation : Tracheal intubation & mechanical ventilation.

e. Heart failure & Hypotension : cardiac support.

f. Treatment of precipitating factors e.g. antibiotics for infections.

Cretinism

Hypothyroidism during infancy

1. **Physiology :** Refer to hyperthyroidism.

2. **Etiology :**

- Congenital.
- Endemic cretinism → iodide deficiency.
- Excess anti-thyroid drugs during pregnancy.

3. **Clinical picture :**

- Persistent physiological jaundice.
- Hoarse cry & feeding problems.
- Disproportionate dwarfism.
- Big lips & protruding tongue & Delayed dentation.
- Delayed walking.
- Muscle weakness (pot belly with umbilical hernia).
- Dry & cold skin.
- Mental deterioration if not treated within 6 months.

4. **Investigation :**

- T4 & T3 : ↓↓
- TSH : ↑↑
- X-ray of carpal bone : delayed appearance of ossification centers

5. **Treatment : Replacement therapy**

- L-thyroxin 0.025 mg/day & ↑↑ dose up to 0.2 mg/day
- It should be started before the 1st 6 months to avoid mental retardation.

Goiter

Definition : Goiter (or goitre) is an enlargement of the thyroid gland.

classification:

i. Simple goiter (Euthyroid goiter) : (non toxic , non inflammatory , non neoplastic)

- Persistent low level of thyroid hormones → ↑ TSH → thyroid enlargement.
 - o Physiological : Puberty , Pregnancy. (due to increased the demand of iodine, so there is relative iodine deficiency)
 - o Iodine deficiency.
 - o Drugs : Anti-thyroid drugs , lithium.
- C/P : Soft symmetrical thyroid swelling.
- Investigations :
 - o Slight elevation of TSH.
 - o Normal thyroid scan & antibodies.
- Treatment :
 - o I2 supplementation.
 - o In young : thyroxin 100 - 150 mcg/d orally to suppress TSH.
 - o In elderly : thyroxin is contraindicated as goitre rarely decreases in size.
 - o Large goiter : surgery (for cosmetic purpose or compression symptoms).

ii. Toxic goiter : (goiter with hyperthyroidism)

- o Diffuse : Grave's disease (1ry thyrotoxicosis)
- o Toxic nodular goiter (2ry thyrotoxicosis , Plummer's disease)

iii. Inflammatory goiter : e.g. Hashimoto's thyroiditis .

iv. Neoplastic goiter.

THYROID CANCER

Certain risk factors for thyroid cancer :

- ☒ It is more common in women (2:1), but men have worse prognosis.
- ☒ It is more likely in a nodule developing in child or patient older than 60.
- ☒ A single hard painless nodule showing rapid growth.
- ☒ Cold nodule in multinodular goiter.
- ☒ History of neck irradiation.
- ☒ Enlarged LNs in the neck region.

Cell type	Frequency	Behavior	Spread	Treatment
Papillary	70%	Commonest. May be multifocal. Occurs in young people (F>M)	- Spreads via lymph nodes. - Local LN metastases occurs even with occult tumors < 1cm.	Total thyroidectomy & adjuvant 131-Iodine. Thyroxin give if hypothyroid and to reduce recurrence. <u>Good prognosis</u>
Follicular	20%	Single encapsulated lesion. Mean age 50 yrs. (F>M)	Spreads via blood, to lung/bone,...	As above
Anaplastic	<5%	<u>Most aggressive.</u> Hard rapidly enlarging. Wt loss, stridor, hoarseness	Locally invasive	Surgery, chemo, radio - <u>useless</u> 80% die within 1 yr.
Lymphoma	2%	Variable		Sometimes responsive to radiotherapy
Medullary cell	5%	Arises from calcitonin secreting parafollicular C cells. Often familial & associated with MEN syndrome.	Lymphatic spread has frequently developed.	- Total thyroidectomy - 131-iodine has no role. - Poor prognosis, but indolent course

Parathyroid gland

Ca metabolism

- Normal Ca level : 8.4 – 10.2 mg%.

A. Ionized (active) : 50%

B. Non-ionized (reserve) : 50%

- 40% bound to albumin. - 10% any other bond (Ca carbonate, phosphate)

Liver cirrhosis & nephrotic syndrome → ↓ albumin → hypocalcaemia ,
but no tetany because ionized Ca is still normal.

- Regulation of Ca :

- Ca level is closely affected & related to P [n. 3 - 4.5 mg%]
- Notice that $Ca \times P = \text{constant [40]}$.
- Serum Ca & P levels are controlled by certain hormones :
 - a. Parathormone.
 - b. Calcitonin.
 - c. Active vitamin D.
- Ca regulation involves 3 sites : bone, intestine & kidney.

	Parathormone*		vitamin D		Calcitonin	
Absorption (intestine)	↑ Ca	↓ P	↑ Ca	↑ P	↓ Ca	
Reabsorption (kidney)	↑ Ca	↓ P	↑ Ca	↑ P	↓ Ca	↓ P
Resorption (bone)	↑ Ca	↓ P	↑ Ca	↑ P	↓ Ca	↓ P
Blood (net result)	↑ Ca	↓ P	↑ Ca	↑ P	↓ Ca	↓ P

*PTH acts directly on bone & kidney & indirectly on intestine (through activation of vit.D).

Hyperparathyroidism

1. Physiology :

- a. Hormone : Parathormone (PTH, 54 amino acid)
- b. Gland : Parathyroid gland.
- c. Function of the hormone : $\uparrow \text{Ca}$, $\downarrow \text{P}$
 - i. GIT : $\uparrow\uparrow$ absorption of Ca (indirectly through vit D)
 - ii. Kidney : $\uparrow\uparrow$ reabsorption of Ca.
 - iii. Bone : $\uparrow\uparrow$ resorption of Ca.
 - iv. $\uparrow$ Renal Phosphate excretion.
- d. Regulation of this hormone :

Hypocalcemia or hyperphosphatemia $\rightarrow \uparrow$ PTH.

2. Etiology :

a. 1ry :

- i. Adenoma of the parathyroid gland. (*most common, 90%*)
- ii. Hyperplasia of the parathyroid gland.
- iii. As a part of **Multiple Endocrine Neoplasia** : MEN-1, MEN-2A

MEN-1 : 3P • Hyper-Parathyroidism : <u>95%</u> • Pituitary tumor : 30% • Pancreatic tumor : 70%	MEN-2A : • Medullary carcinoma of thyroid 90% • Pheochromocytoma 40% • Hyperparathyroidism 25%
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b. 2ry : Due to $\downarrow \text{Ca}$ as in **Chronic renal failure** & malabsorption syndrome.

c. 3ry : usually in end stage CRF

- Longstanding 2ry hyperparathyroidism $\rightarrow$ irreversible parathyroid hyperplasia. (start 2ry $\rightarrow$ end 1ry)
- Parathyroidectomy is the only appropriate treatment.

d. Paramalignant syndrome (oat cell carcinoma).

3. C / P : 50% → **asymptomatic**, more common in ♀ > 50 y

Disease of bone, renal stone, abdominal groans & psychic moans 🎵🎵

i. Bone : (Ostitis fibrosa cystica)

1. **pain.**
2. **pathological fracture.**

Ostitis fibrosa cystic : *Fibrous degeneration & cysts formation* (🎵) due to osteoclastic activity secondary to hyperparathyroidism.

ii. Renal :

1. Repeated **stones.**
2. Polyuria (Ca diabetes) & polydipsia.
3. Nephrocalcinosis & renal failure may occur.

iii. Others : 4 X 2

1. **CNS :**
 - a. **Drowsiness.**
 - b. **Depression.**
2. **GIT :**
 - a. **Peptic ulcer & Pancreatitis (abdominal pain).**
 - b. **Constipation.**
3. **CVS :**
 - a. **ECG : short Q-T interval & arrhythmia.**
 - b. **Hypertension.**
4. **Skin :**
 - a. **Dry.**
 - b. **Itching.**

- **Ca > 11mg%. → Clinical manifestations of Ca**
- **Ca > 13mg%. → Renal impairment**
- **Ca > 14 mg% → Coma & cardiac arrest (endocrinal emergency)**

4. **D. D. of hypercalcemia :** (4 X 3)

a. Endocrine :

- i. Hyperparathyroidism (1ry & 3ry). The most common cause
- ii. Hyperthyroidism.
- iii. Addison's disease (Cortisone → -- vit.D).

b. Malignancy :

- i. Bronchogenic carcinoma .
- ii. Multiple myeloma.
- iii. Lymphoma → activation of vitamin D.

c. Bone :

- i. T.B.
- ii. Sarcoidosis.
- iii. Immobilization.

d. Others :

- i. Hypervitaminosis (vitamin D).
- ii. Drug induced : **thiazide** , **lithium**.
- iii. Familial hypocalciuric hypercalcemia.

5. Investigation :

a. Investigations for the cause : Parathyroid imaging: CT, MRI , radioisotope scan

b. Assay of the hormone level : parathormone : ↑↑ [n: 0.5 – 1 ngm/ml]

c. Investigations of the function of the hormone :

i. Blood :

	1ry	2ry	3ry
1. Ca	↑	↓	↑
2. P	↓	↑	↑
3. Alkaline phosphatase	↑	↑↑	↑↑↑

NB : *Persistent hypercalcemia , hypo P & an elevated PTH confirm the diagnosis of 1ry hyperparathyroidism.*

ii. Urine :

1. ↑ Ca [n: 150 mg / day] & ↑ P [n: 1 gm / day]
2. ↑ hydroxyproline & c-AMP due to ↑ bone resorption.

iii. **X-ray :**1. **bone :**

- a. **Loss of lamina dura of the teeth. (the earliest sign)**
- b. Subperiosteal bone resorption in the distal phalanges & distal end of clavicle.
- c. Ground glass appearance of the bones (Osteopenia)
- d. Skull → mottling of the skull. (*salt & pepper skull*).
- e. Spine → cod fish spine (indentation of vertebrae by discs)

2. **renal :** urinary stones , nephrocalcinosis.iv. **Bone biopsy :** osteomalacia with excess osteoclasts.d. **Suppression test :** (**steroid test**)

- i. +ve (↓ Ca level) → normal.
- ii. -ve (no suppression) → Hyperparathyroidism.

6. Treatment :a. **Surgery:** Removal of the parathyroid glands with Ca & vit D supply.**2008 guideline for surgery :**

- Serum Ca : > 1mg% above upper limit of normal.
- Creatinine clearance : < 60ml/min
- BMD : T-score < -2.5 at any site and/or previous fracture fragility.
- Age : < 50 years.

b. **Medical treatment of hypercalcemia :**

- i. ↓ intake & ↑↑ fluid intake.
- ii. ↓ absorption : by oral phosphate.
- iii. ↑ loss of Ca : saline then furosemide or dialysis in sever cases.
- iv. Calcitonin.
- v. β-blocker : ↓ the adverse effect of hypercalcemia on the heart
- vi. Cortisone is effective in some cases (related to vitamin D excess)
- vii. Alendronate (Osteomax) : ↓↓ osteoclastic activity.

Hypercalcemic crisis (serum Ca level > 14 mg %)**a. Manifestations** (non secific) :

- i. *GIT* : Nausea , vomiting , constipation & abdominal pain.
- ii. *Renal* : Polyuria & dehydration.
- iii. *CNS* : Confusion & coma.
- iv. *CVS* : Arrhythmia , shortened QT interval.

b. Treatment :

- i. **IV normal saline** : 4-6 L/day may be necessary. (the first goal)
- ii. **Lasix** (40 – 80 mg IV every 2 hours) , Should **NEVER** be administrated without saline infusion, or else dehydration will be aggravated.
- iii. IV pamidronate (*Aredia*) : drug of choice.
It inhibits the osteoclastic activity. Dose : 30 - 90 mg IV infusion over 24 h.
- iv. Calcitonin : it inhibits bone resorption & has hypercalciuric effect.
- v. Cortisone : is the first line of treatment for hypercalcemia caused by vitamin D excess e.g. myeloma, lymphoma, sarcoidosis, but is NOT beneficial in hyperparathyroidism.
- vi. Dialysis is effective in removing Ca in patients with renal failure.

Success usually comes to those who are too busy to be looking for it

Henry David Thoreau

Hypoparathyroidism

(Tetany)

Definition of tetany :

State of $\uparrow\uparrow$ neuro-muscular irritability due to: $\downarrow$ ionized Ca , $\downarrow$ Mg or alkalosis.

Etiology of tetany : ($\downarrow$ ionized Ca , $\downarrow$ Mg or alkalosis)

a. Hypocalcaemia :

i. Hypoparathyroidism :

1. Surgery removal.
2. Irradiation.
3. Di- george syndrome : absent parathyroid & thymus glands.
4. Pseudo hypoparathyroidism (resistance of PTH)

ii. $\downarrow$ Ca intake : starvation.

iii. $\downarrow$ Ca absorption :

1. malabsorption syndrome.
2. $\downarrow$ active vitamin D.

iv. Precipitation of Ca in tissue e.g. acute pancreatitis.

v. $\uparrow$ Ca excretion : **CRF (most common cause of hypocalcemia).**

N.B. tetany rarely occurs in RF because of acidosis which convert non ionized Ca into ionized Ca.

b. **Hypomagnesaemia** : Excess diuretic , Malabsorption syndrome.

c. **Alkalosis** : (Ionized Ca $\rightarrow$ non ionized Ca).

i. Respiratory alkalosis : any case of hyperventilation :

ii. Metabolic alkalosis :

1. loss of HCl : vomiting , gastritis , gastrectomy.
2. milk alkali syndrome.
3. hypokalemia e.g. Conn's syndrome.

hypokalemia (**K loss**) $\leftrightarrow$ Al-**K-Lossis** 😊

C / P of Tetany :iii. **Latent tetany :** (serum Ca = 7 – 9 mg%)

1. manifestations of tetany are not present.
2. manifestations appear by provocative tests :
 - a. **Chvostek's test :**
tapping over the facial nerve → contraction of the facial muscles.
 - b. **Trousseau's test :**
Inflation of a BP cuff above SBP for 3 minutes → carpal spasm.
 - c. **Erb's test :** (normally : 8 mili-amperes at least are needed for stimulations)
electric current < 4mili-amperes → muscle contraction.

iv. **Manifest tetany :** (serum Ca < 7 mg%)

1. Irritability & parasthesia around mouth & fingers.
2. Muscle twitches & may be convulsion in severe cases.
3. **Spasm :**
 - a. eye lids : blepharospasm.
 - b. mouth : trismus of jaw.
 - c. larynx : laryngospasm.
 - d. **carpo-pedal spasm.**
 - e. diaphragm : Hiccough.
 - f. GIT : abdominal colic.
4. Cardiovascular : QT prolongation , refractory HF , hypotension.
5. On ectodermal structures : (*only in hypocalcemia*)
brittle nail , hypoplastic teeth , cataract.

Investigation : (for the cause)

- In hypoparathyroidism : ↓ PTH , ↓ serum Ca , ↑ P.
- In hypomagnesaemia : **Refractory hypokalemia.** MCQ
- In alkaosis : ↑ PH , ↓ ionized Ca.

Treatment :

- a. Acute attack : IV **Ca gluconate** 10 ml 10% very slowly.
- b. **Treatment of the cause :**
 - Hypocalcemia : oral Ca , vitamin D
 - Hypomagnesaemia : oral Mg.
 - Alkalosis : Treatment of the cause , acidifying drugs.

Pseudo-hypoparathyroidism : (PHP)**MCQ**

- Here, the level of PTH is high but there is resistance to all its action.
- So, there are hypocalcemia & hyperphosphatemia.
- It's a genetic disorder.
- There are 3 different forms :

➤ PHP type 1a :

- o Albright's hereditary osteodystrophy : short stature, round face, and short hand bones.
- o Manifestations of hypocalcemia.

➤ PHP type 1b :

- o Resistance to PTH only in the kidneys.
- o Normal appearance + clinical picture of hypocalcemia.

➤ Pseudopseudohypoparathyroidism : I think it is the longest word in English ☺

- o The same presentation as type 1a, but is biochemically normal.
- o Hormone resistance is not present.

Suprarenal gland

(Adrenal gland)

- There are 2 adrenal glands at the superior pole of each kidney.
- They are composed of outer cortex & inner medulla :
 - i. Adrenal cortex (the outer part) which is formed of 3 separate layers :
 - o **Zona Glomerulosa** : secretes aldosterone (mineralocorticoids).
 - o **Zona Fasciculata** : secretes cortisol (glucocorticoids)
 - o **Zona Reticularis** : secretes androgen.
 - ii. Adrenal medulla (the inner part) : secretes catecholamines.

Disorders of suprarenal gland :

➤ Hyperfunction of adrenal cortex :

- o **Conn's syndrome** : ↑ aldosterone.
- o **Cushing syndrome** : ↑ Cortisol.
- o **Adrenogenital hyperplasia** : ↑ androgen.

➤ Hyperfunction of adrenal medulla : Pheochromocytoma.

➤ Adrenal cortical hypofunction : Addison's disease (1ry adrenal failure)

Conn's syndrome

(1ry hyperaldosteronism)

1. Physiology :

- a. **Hormone** : Mineralocorticoid (Aldosterone).
- b. **Gland** : Suprarenal gland (*Zona glomerulosa*).
- c. **Function** : reabsorb Na & excrete K & H⁺
 - i. ↑ Na , ↑ H₂O.
 - ii. ↓ K , ↓ H⁺.
- d. **Regulation** : Aldosterone secretion is stimulated by :
 - i. Hypovolemia → ↑ **Renin** → ↑ aldosterone
 - ii. ↑ K (hyperkalemia) & ↓ Na (hyponatremia)
 - iii. A.C.T.H. → during stress only.

2. Etiology :

- a. Unilateral adenoma of zona glomerulosa : 60% of cases.
- b. Bilateral hyperplasia : 30%
- c. Paraneoplastic syndrome.

3. Clinical picture :

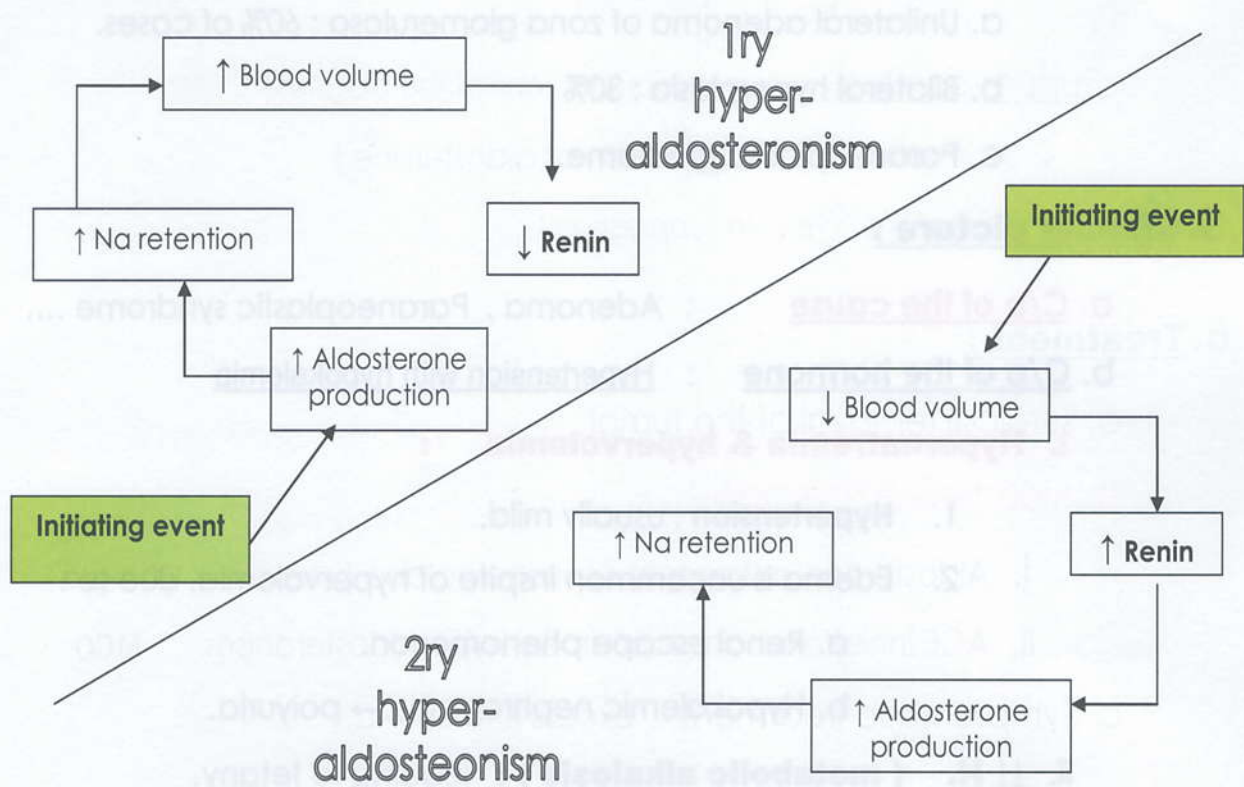
- a. **C/p of the cause** : Adenoma , Paraneoplastic syndrome
- b. **C/p of the hormone** : Hypertension with hypokalemia
 - i. **Hypernatremia & hypervolemia** :
 - 1. **Hypertension** : usually mild.
 - 2. Edema is uncommon inspite of hypervolemia, due to :
 - a. Renal escape phenomenon.
 - b. Hypokalemic nephropathy → polyuria.
 - ii. ↓↓ **H. (metabolic alkalosis)** : leading to tetany.

iii. **↓ K. (hypokalemia) : muscles**

- 1. **Skeletal muscles** : weakness, muscle cramping.
- 2. **Smooth muscles (GIT)** : atony, constipation.
- 3. **Cardiac muscle** : arrhythmia , ECG changes (prominent U wave)
- 4. **Others** : polyuria, paraesthesia.

4. **Differential diagnosis** : form 2ry hyperaldosteronism (stimulus is extra-adrenal)

	1ry hyperaldosteronism	2ry hyperaldosteronism
Source	- Adrenal Gland.	- Renal artery stenosis. - Heart failure. - Nephrotic syndrome. - Liver cirrhosis.
Aldosterone	+++	+
Renin	↓↓	↑↑
HTN	mild.	No HTN except in renal artery stenosis → sever.



5. Investigation : HIGH ALDOSTERONE, LOW RENIN, LOW K

a. Investigations for the cause : suprarenal gland imaging : US , CT , MRI

b. Assay of the hormone level :

i. In blood :

1. ↑ **aldosterone** in serum ($n = 3-15 \text{ ngm\%}$).
2. ↓ **plasma renin** activity (due to -ve feed back)

ii. In urine :

High urine aldosterone (tetrahydroaldosterone)

c. Investigation for the function of aldosterone :

i. Blood :

1. ↓ **K.** (**hypokalemia**, $<3.5 \text{ mEq/L}$)
2. ↑ Na.
3. alkalosis : ↑ serum HCO_3

Again, Hypertension with hypokalemia

ii. Urine : ↓ Na, ↑ K, ↑ H^+

d. Suppression test : saline infusion, to confirm the diagnosis.

- Normally : +ve (suppression of aldosterone)
- In Conn's : -ve (No suppression)

6. Treatment :

a. Surgical removal of the tumor.

b. Aldosterone antagonist :

- i. Aldosterone antagonist : spironolactone (aldactone 400 mg/d)
- ii. ACE inhibitors : captopril in 2ry hyperaldosteronism. **MCQ**

c. Symptomatic treatment : excess K & low Na.

Cushing's syndrome

1. Physiology :

a. Hormone : ↑ Cortisol (glucocorticoid)

b. Gland : Suprarenal gland (Zona fasciculata)

c. Function of the hormone : 10

- i. CHO : hyperglycemia.
- ii. Protein : catabolic.
- iii. **Fat** :
 1. lipolytic.
 2. Redistribution of fat in abnormal sites (face, back of neck, trunk)
- iv. Water & electrolyte : (aldosterone like)
 1. ↑ H₂O & Na.
 2. ↓ K & H⁺.
- v. **Stomach** : ↑ HCl
- vi. **Bone** : anti-vitamin D action.
- vii. **Blood** : (2 ↑↑ & 3 ↓↓) MCQ
 1. ↑ RBCs.
 2. ↑ neutrophils.
 3. ↓ lymphocytes.
 4. ↓ esinophils & basophilis.
- viii. Psychosis.
- ix. Androgenic action.
- x. Anti-inflammatory & anti-allergic.

d. Regulation of the hormone : stimulated by ACTH.

2. Etiology :

I. **ACTH dependent** : ACTH > 15pg/dl

- a. **Pituitary adenoma** (pituitary Cushing, Cushing disease or 2ry Cushing) :
basophil adenoma of pituitary gland → secreting ACTH [70 %].
- b. **Paramalignant syndrome** e.g. oat cell carcinoma. (Ectopic ACTH secretion).

II. **ACTH independent** : Undetected ACTH with elevated cortisol > 15mcg/dl

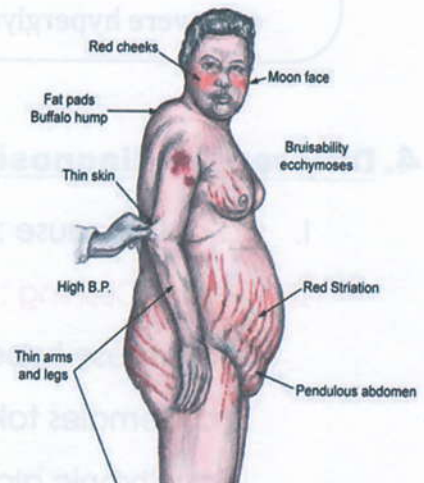
- a. **Adrenal adenoma** : 1ry Cushing or Cushing syndrome.
- b. **Exogenous glucocorticoid therapy**. (Cushinoid picture).

3. Clinical picture :

- a. C / p of the cause : Pituitary tumor , Paraneoplastic syndrome.

b. C / p of the hormone :

- i. **CHO** : Glucose intolerance & may be secondary DM in 15 %.
- ii. **Protein** : catabolic
 1. Muscle wasting & weakness.
 2. Capillary fragility : purpura.
 3. Osteoporosis.
 4. Thinning of skin, stria rubra, delayed wound healing.
- iii. **Fat** : abnormal deposition of fat :
 1. Face : moon face with acne.
 2. Inter-scapular area : buffalo hump.
 3. Trunkal obesity with thin limbs (samboxa shaped obesity)
- iv. **Water & electrolyte** : $\uparrow \text{Na, H}_2\text{O}$ & $\downarrow \text{K, H}^+$
 1. HTN (due to $\uparrow \text{Na}$ & $\uparrow$ the action of catecholamines)
 2. Manifestations of hypokalemia.
 3. alkalosis.



- v. **Stomach** : peptic ulcer (perforation).
- vi. **Bone** : osteomalacia & osteoporosis.
- vii. **Blood** : polycythemia (plethoric face) , Recurrent infections due to diminished function of neutrophils.
- viii. **Psychiatric** : depression & suicidal tendency.
- ix. **Androgenic action** :
 - 1. Female : amenorrhea, hirsutism.
 - 2. Male : ↓ libido , impotence & hirsutism.
- x. **Skin pigmentation** only in **Secondary** (ACTH dependent)
Cushing due to ↑ ACTH

Causes of death : Cardiovascular disease & infections.

Features suggest ectopic ACTH secretion (Paraneoplastic syndrome) :

- Short duration.
- Weight loss rather than weight gain.
- Severe hypokalemia.
- Severe hyperglycemia (DM)



4. Differential diagnosis :

I. DD of the cause : 1ry & 2ry Cushing.

II. **Pseudo Cushing** : MCQ

- a. Obese hypertensive diabetic patients.
- b. Females taking oral contraceptive pills.
- c. Chronic alcoholism → impaired liver function → impaired metabolism of corticosteroids.
- d. Depression.

5. Investigation :

a. Assay of the hormones level :

i. In blood :

1. cortisolone : $\uparrow$ (N : 5 – 20 $\mu\text{g} \%$)

a. Early : loss of circadian rhythm (no $\downarrow$ of cortisol level by night).

b. Later : persistent high level.

Single random cortisol level is not reliable.

2. ACTH : (N : 60 pg/ml)

a. $\uparrow$ $\rightarrow$ pituitary Cushing or Paramalignant syndrome.

b. $\downarrow$ $\rightarrow$ adrenal Cushing.

ii. In urine : 24-hours urine free cortisol

High in Cushing's syndrome, depression & obesity. This is the single best biochemical marker of Cushing syndrome. **MCQ**

b. Investigations for the cause :

i. CT scan of the adrenal if the ACTH is low.

ii. If the ACTH is high : MRI of the pituitary or CT of the chest looking for an ectopic focus.

iii. Inferior petrosal venous sampling of ACTH : is an invasive procedure used to confirm pituitary origin of the tumor in difficult cases.

c. Investigations of the function of cortisolone :

i. Biochemical changes : $\downarrow\text{K}$, $\uparrow\text{Na}$, $\uparrow\text{glucose}$.

ii. Blood picture : $\uparrow\text{RBCs}$, neutrophils & $\downarrow\text{lymphocytes}$, esinophils.

d. Suppression test : (Dexamethazone test).

1. Low dose : 1mg overnight oral dexamethazone test

i. Normal response : +ve (morning suppression of cortisol level $< 5 \mu\text{g} \%$)

ii. -ve (no suppression, plasma cortisol $> 5 \mu\text{g} \%$) : In Cushing, depression or obesity.

Initial step : overnight
dexamethazone suppression test
confirmed by 24 h urine free cortisol

2. **High dose : 2 mg / 6h → for 2days.**

- i. +ve (↓ cortisol level by more than 50% of the baseline) → **2ry (pituitary)** Cushing.
- ii. -ve (no suppression) → 1ry Cushing & ectopic ACTH secretion.

6. Treatment :

I. Surgery :

- Surgical resection of the pituitary, adrenal or ectopic ACTH producing tumor, followed by replacement therapy.
- **Nelson syndrome** : big pituitary adenoma with very high ACTH & hyperpigmentation after bilateral adrenalectomy in a case of pituitary Cushing.

II. Irradiation :

Less effective than surgery, reserved for high surgical risk patients.

III. Medical : (Steroid antagonists) **MCQ**

- a) Aminoglutethimide : Antisteroid drug
- b) Mitotane : anti-neoplastic drug used in the treatment of adrenocortical carcinoma.
- c) Metyrapone : it blocks cortisol synthesis by inhibiting steroid 11β-hydroxylase.
- d) Ketoconazole : antifungal & also has antiglucocorticoid effects.

Medical adrenalectomy is done by all EXCEPT

- a) Aminoglutethimide.
- b) Mitotane.
- c) Mexiletine.
- d) Metyrapone.

Answer : C, Mexiletine : Class IB anti-arrhythmic.

Adrenogenital syndrome

(Congenital adrenal hyperplasia)

1. Physiology :

- a. Hormone : Sex hormone (androgen).
- b. Gland : Suprarenal gland (zona reticularis).
- c. Function of the hormone : Gametogenesis & 2ry sex characters.
- d. Regulation of this hormone : ACTH.

2. Etiology :

Enzyme deficiency in the cortical synthetic pathways (21 hydroxylase enzyme) $\rightarrow$ $\downarrow$ cortisol level $\rightarrow$ $\uparrow$ ACTH $\rightarrow$ act on zona reticularis $\rightarrow$ $\uparrow$ sex hormone secretion

3. C / P : depends on age & sex of the patient.

- a. Pre-natal : Female pseudohermaphroditism :
(small vagina, big fused labia majora simulating scrotum)
- b. Post-natal & before puberty :
 - i. In males : pseudo-precocious puberty (masculinization, deepening of voice, but with small testis & no spermatogenesis)
 - ii. In females : virilism (amenorrhea, masculinization & hirsutism)

N.B. : Hirsutism before menarche is suggestive for congenital adrenal hyperplasia.

- c. After puberty : there is virilism in females.

4. Investigation :

- a. Investigations for the cause : Imaging for the gland.
- b. Assay of the hormones level :
 - i. In blood : $\uparrow$ testosterone , $\uparrow$ ACTH.
 - ii. In urine : $\uparrow$ metabolite of testosterone (17-hydrotestosterone).

5. Treatment : Cortisone $\rightarrow$ Suppress ACTH $\rightarrow$ $\downarrow$ Androgens.

Chronic Adrenal Failure

(Addison's disease, adrenal insufficiency)

Failure of the adrenal cortex leads to a decrease in its hormones.

- Primary adrenal insufficiency : **Addison disease**.
- Secondary adrenal insufficiency : pituitary disease (panhypopituitarism)
- Tertiary : hypothalamic disease.

1. Etiology of primary adrenal failure:

- a. **Idiopathic atrophy**, most probably **Autoimmune** : the most common 80%
- b. **Tuberculosis** → 15%
- c. Surgery & Irradiation.
- d. Sarcoidosis & Hemochromatosis. 🎵🎵
- e. Adrenal hemorrhage : in meningococcal septicemia.

2. C / P : The gradual & nonspecific symptoms often lead to an incorrect initial diagnosis.

a. C / p of the cause :

Associated with other autoimmune diseases : e.g. type 1 DM, thyroid disease, vitiligo (*polyglandular autoimmune syndrome*)

b. C / p of the hormone :

i. **Hypoglycemia** : (due to ↓ cortisone)

1. Drowsiness, lack of concentration, hunger pain, coma.
2. There may be absence of the usual warning signs due to lack of adrenaline (notice that ↓ cortisone → ↓ action of catecholamine)

ii. **Hypotension** : (due to ↓ cortisone & aldosterone)

1. ↓ Cortisol & aldosterone → ↓ Na → Hypovolemia & decreased response of the blood vessels to the action of catecholamines → hypotension.
2. Postural hypotension is common due to ↓ action of catecholamine.

iii. **Hyper-Pigmentation** : (due to high level of ACTH in **P**Primary adrenal failure)

1. $\uparrow\uparrow$ ACTH $\rightarrow$ direct action on melanocytes.
2. It is not present in secondary adrenal failure.

3. Site :

a. Sun exposed areas : face & neck.

b. Friction & pressure areas : elbow.

c. Pigmented areas : areola.

d. Recent scars & nails.

e. Mucous membrane : mouth & tongue.



iv. **GIT manifestations** :

1. Anorexia, nausea, vomiting.
2. Alternating diarrhea and constipation.
3. **Abdominal pain** : due to $\downarrow$ Na , tender renal angle due to TB.

v. **Asthenia** : marked muscle weakness, fatigue & weight loss (100%)

1. $\downarrow$ aldosterone $\rightarrow$ hyperkalemia & hyponatremia.
2. $\downarrow$ cortisol $\rightarrow$ hypoglycemia.
3. $\downarrow$ androgens $\rightarrow$ -ve nitrogen balance.

vi. **Others** :

1. Polyuria : due to Na diuresis.
2. Neuropathy.
3. Deficiency of adrenal androgen : manifests in females only, resulting in loss of axillary and pubic hair (both are under influence of adrenal androgen only in females).

vii. **Complications** : **"Addisonian crisis"** see later

3. Differential diagnosis :

a. 2ry adrenal insufficiency :

- Hypopituitarism $\rightarrow$ $\downarrow$ ACTH $\rightarrow$ $\downarrow$ cortisone & $\downarrow$ androgen with no $\downarrow$ aldosterone.

- In 2ry adrenal failure there are :

- No skin pigmentation. (due to $\downarrow$ ACTH)
- Minimal hypotension (due to normal aldosterone).
- Manifestations of panhypopituitarism.

b. Skin pigmentation :

- Endocrinal diseases : 1ry Addison , 2ry Cushing , DM , thyrotoxicosis.
- Chronic renal failure. – Skin diseases
- Malignancy. – Pregnancy. 🎵🎵
- Hemochromatosis. – 1ry biliary cirrhosis. 🎵🎵

4. Investigation : Low cortisol level < 5 $\mu\text{g/dl}$ confirmed by ACTH stimulation test

a. Investigations for the cause :

- i. Imaging for suprarenal gland : Abdominal U/S , CT, MRI.
- ii. Adrenal antibodies : in autoimmune cases.
- iii. Chest X-ray : may show evidence of old or active TB.
- iv. Investigations for thyroid disease & DM should be done in suspected polyglandular autoimmune syndrome.

b. Assay of the hormones level :

1. **Low morning cortisol level < 5 $\mu\text{g/dl}$ is highly suggestive.** The diagnosis of AI is ruled out if morning cortisol level > 18 $\mu\text{g/dl}$
2. ACTH level : elevated (≥ 50 pg/mL) in 1ry adrenal failure, $\downarrow$ in 2ry adrenal failure.
3. Aldosterone is deficient in primary AI & not deficient in 2ry adrenal failure as it is under control of renin not ACTH.

c. Investigations of the functions :**i. Biochemical changes :**

- Serum Na : ↓ (< 135 mEq/L)
- Serum K : ↑ (> 5 mEq/L)
- Fasting glucose : < 50 mg/dl
- HCO₃ : < 15 mEq/L (metabolic acidosis)
- BUN : > 20 mg/dl due to prerenal azotemia secondary to hypovolemia.

ii. Blood picture : MCQ

1. ↓ Neutrophils.
2. ↑ Lymphocytes, esinophils, basophils .

d. Stimulatory test : ACTH stimulation test

- **It is the best diagnostic tool to confirm the diagnosis.**
- Synacthen (synthetic ACTH) 250 mcg IV or IM followed by measurement of serum cortisol levels at 0 , 30 , 60 minutes.
 - Normal response : +ve (↑ cortisol level > 18 µg/dl)
 - 1ry Adrenal failure : -ve response (cortisol level < 18 µg/dl)

5. Treatment :

a. Treatment of the cause e.g. TB.

b. Diet : ↑ (Na , CHO & protein).

c. Replacement therapy :**i. Glucocorticoid replacement :**

- ✗ Hydrocortisone 20 mg am, 10 mg pm. Or
- ✗ Prednisolone 5 mg am, 2.5 mg pm. Or
- ✗ Dexamethasone 0.5 mg am & 0.25 mg pm.

ii. Mineralocorticoid replacement : Fludrocortisone : 0.1 mg/d to replace aldosterone, especially in severe hypotension.

During stress (Infection or Surgery) :

- Intercurrent infection : The dose of hydrocortisone is doubled.
- Surgery : premedication with 100 mg hydrocortisone IM, then 100 mg/6h IM for one day in a minor surgery (e.g. hernia) & for 3 days in a major surgery.

Adrenal crisis*(Acute adrenal failure)*

It is a **medical emergency**, that may be fatal if not recognized and treated immediately.

Etiology :**i. Acute on top of chronic :**

1. Addison's disease subjected to : surgery , infection, bleeding.
2. Panhypopituitarism : if treatment is initiated with thyroxin.

ii. Acute from the start :

1. Surgery : bilateral adrenalectomy.
2. Sudden withdrawal of chronic cortisone therapy.
3. Meningococcal septicemia (Waterhouse-Freidrichon's syndrome)
4. Massive thrombosis of adrenal vein.

C / P :

a. C / p of the cause : Surgery, Infection.

b. C / p of the hormone :

- | | |
|-----------------------------------|--------------------------------|
| 1. <i>Sever hypoglycemia</i> | → coma. |
| 2. <i>Sever hypotension</i> | → shock. |
| 3. <i>Sever asthenia</i> | → confusion. |
| 4. <i>Sever skin pigmentation</i> | → desquamation. |
| 5. <i>Sever diarrhea</i> | → dehydration & acute abdomen. |

Investigation : As Addison's disease.

Acute adrenal failure should be suspected in any patient in the ICU who develops hypotension of unclear etiology or has refractory hypotension (*hypotension not corrected by saline & vasopressors*)

Treatment : (S-S-S) Steroid, Sugar, Saline ☺

i. IV fluids :

- 1 - 2 L of normal saline (0.9 % NaCl).
- 1 - 2 L of 10% glucose.

ii. Cortisone is started immediately as follow :

- Hydrocortisone, 50 - 100 mg /6 h **IV** until the patient is clinically stable then shift to oral cortisone.
- Dexamethasone (Decadron) can be given before or during the ACTH stimulation test. *It will not interfere with plasma cortisol assay.*
- Fludrocortisone is NOT needed during adrenal crisis as glucocorticoids in high dose have mineralocorticoid effects.

iii. Treatment of the precipitating factors : e.g. infection or DIC.

Pheochromocytoma

(Hyperfunction of adrenal medulla)

- It's the commonest tumor arising from the adrenal medulla.

- **Rule of 10 :**

- 10 % familial.
- 10 % bilateral.
- 10 % malignant.
- 10 % extra-adrenal (in the sympathetic chain).

C / P :



- a. Paroxysmal hypertension.
- b. Paroxysmal headache.
- c. Paroxysmal sweating.
- d. Paroxysmal tachycardia (palpitation)
- e. Anxiety & psychiatric disturbance.

Investigation :



- a. Urinary $\uparrow\uparrow$ VMA (Valenyle Mandelic Acid) : $\uparrow$
- b. Urinary catecholamine : $\uparrow$
- c. Plasma catecholamine : $\uparrow$
- d. CT scan , MRI for abdomen.
- e. Radioisotope scanning : scanning with **Meta Iodo Benzyl Guanidine** (**MIBG**) produces specific uptake in sites of sympathetic activity.

Treatment :

- a. Surgery is the treatment of choice.
- b. Medical : combined α & β blockers.

☠ If you start with β blocker $\rightarrow$ unopposed α action $\rightarrow$ Hypertensive crisis.

Steroid preparations

Uses :

1. Replacement therapy :

- a. Addison's disease.
- b. Congenital adrenal hyperplasia.

2. Supplementary therapy in non endocrine diseases :

a. Anti-inflammatory & anti-allergic :

i. CNS :

1. cerebral edema with neoplasm.
2. ↑ ICT.

ii. CVS :

1. rheumatic fever.
2. Post infarction syndrome (Dressler's syndrome)
3. hemolytic anemia.
4. ITP.

iii. GIT :

1. ulcerative colitis & Crohn's disease.
2. chronic hepatitis.

iv. Respiratory :

1. bronchial asthma .
2. COPD.
3. sacroidosis.

v. Renal : certain types of GN.

vi. Collagen disease : SLE , polymyositis ,PAN , Rh.arthritis.

vii. Allergic disease : anaphylaxis.

viii. Inflammatory conditions :

1. eye → conjunctivitis.
2. skin → eczema.

b. Anti-stress & anti-shock.

3. Suppression therapy :

- a. Tissue transplantation.
- b. Lymphoma & leukemia.

Side effects & contraindications :

	Side effect	Contraindication
1. From prolonged treatment		
<u>a- Metabolism :</u>		
▪ CHO	- Hyperglycemia.	- D.M.
▪ Fat	- Moon face. - Buffalo hump.	- Cushing syndrome.
▪ Protein	- Osteoporosis. - muscle weakness.	- Myopathy. - Wasting.
▪ Electrolytes	- Na & water retention. - Hypokalemia. - Hypocalcaemia.	- Hypertension. - Hypokalemia. - Rickets & osteoporosis.
<u>b- Systems :</u>		
▪ General	- Delay healing of wound.	- Uncontrolled infection.
▪ Eye	- Cataract. - Glaucoma.	- Cataract. - Glaucoma.
▪ CNS	- Nervousness. - Insomnia. - Psychosis.	- Psychosis.
▪ CVS	- HTN. - HF. - Thrombosis.	- HTN. - HF.
▪ Respiratory	- Chest infections.	- T.B.
▪ GIT	- ↑ Gastric acidity.	- Peptic ulcer.
▪ Genital	- Teratogenecity. - Menstrual disturbance. - Hirsutism.	- Pregnancy.
2. From sudden withdrawal of steroids		
	- Adrenal crisis.	- Sudden withdrawal.

Diabetes mellitus

Definition :

It's a **clinical syndrome** in which there is an error of CHO metabolism ; due to absolute or relative insulin deficiency, ending in chronic hyperglycemia, glucosuria, vasculopathy, neuropathy & disturbed fat & protein metabolism.

Etiology: (1ry → 95% & 2ry → 5%)

1. Primary : (includes 3 types :)

- a. Type 1 : previously called **Insulin-Dependant DM** (IDDM) or juvenile-onset DM.
- b. Type 2: previously called **non insulin-dependant DM** (NIDDM) or adult-onset DM.

c. Special types :

➤ **MODY : Mature Onset Diabetes in Young patient.**

- MODY is the term used to describe type 2 diabetes occurring in patients under the age of 25 with a strong family history. MODY does not always require insulin treatment.
- It is due to single gene defect with an autosomal dominant mode of inheritance. (monogenic form of diabetes).
- There are 6 variants : MODY 1, 2, 3, 4, 5, 6 due to different gene mutation. All of which limit the ability of the pancreas to produce insulin.

➤ **LADA : Latent Autoimmune Diabetes of the Adult.**

A condition in which Type 1 diabetes develops in adults. Here, the autoimmune β cell destruction is slow. So, it is frequently initially misdiagnosed as having Type 2 diabetes.

The old classification of insulin dependant & non-insulin dependant DM is misleading because many patient type 2 DM eventually require insulin for control hyperglycemia.

II. Secondary :

a. Pancreatic causes e.g. Chronic pancreatitis, Hemochromatosis.

b. Endocrinal :

- Cushing.
- Thyrotoxicosis.
- Somatostatinoma , glucagonoma.
- Acromegaly.
- Pheochromocytoma.

c. Drugs : β agonists, Cortisone, Thiazide, Contraceptive pills.

d. Genetic syndromes sometimes associated with diabetes :

- Down's syndrome.
- Friedreich's ataxia.
- Turner's syndrome.
- Myotonia dystrophy

e. Others : Gestational diabetes , Rubella, DIDMOAD syndrome.

Pathogenesis :

Type 1 : 15 %.

- An **autoimmune** destruction of the pancreatic β -cells leads to absolute insulin deficiency.
- Genetic factor play an important role (*the combination of HLA **DR3** & **DR4** makes a person more likely to develop type 1 DM*)
- Viral infection may play a role.
- Without insulin, these patients are prone to develop ketoacidosis.
- Although typically diagnosed before age 30, it can present at any age due to variability in rate of β -cell destruction. (Peak incidence is at about 12 years of age).

Type 2 : 85 %

- It's characterized by peripheral insulin resistance, so hyperglycemia develops despite above average level of insulin.
- In addition, it may be due to abnormal structure of insulin or due to anti-insulin hormones e.g. glucagons.
- Factors that may play a role in pathogenesis include : genetic predisposition & obesity.

	Type 1	Type 2
▪ Incidence :	15 %	85%
▪ Pathogenesis :	Insulin deficiency due to damage of β -cells.	Insulin resistance.
▪ Insulin level :	$\downarrow\downarrow$	Normal or even $\uparrow\uparrow$
▪ Age of onset :	Younger (usually < 30y).	Older (usually > 30y).
▪ Body weight :	Thin.	Obese (usually 80 %).
▪ HLA association	HLA DR3/4	No HLA association.
▪ Hereditary :	- 30% in identical twins - Usually no family history. - Both parents affected : 10% risk for child.	- Near 100% in identical twins. - Strong family history. - Both parents affected : 70-100% risk for child.
▪ C / P :		
- Severity :	Sever.	Mild or moderate.
- Ketoacidosis :	Common.	Rare, need ppt factors.
- Complication :	More common.	Less common.
▪ Autoantibodies :	- Islet cell Ab (ICA). - GAD (Glutamic acid decarboxylase) Ab.	No association with antibodies.
▪ Treatment :		
- Oral hypoglycemic	Ineffective.	Effective.
- Insulin :	Necessary (essential for life)	Usually not required

Stages of DM :

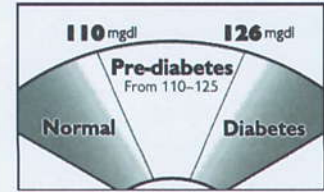
I. Pre diabetes : (IFG, IGT)

- Pre-diabetes is a condition in which blood glucose levels are higher than normal but not high enough for a diagnosis of diabetes. This condition is sometimes called impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the test used to diagnose it.
- It's an intermediate category between normal & DM.

c. There is a risk for future diabetes & CVS diseases.

d. Criteria for diagnosis of prediabetes :

- IFG : 100 – 125 mg%
- IGT : 140 – 199 mg%
- Hb A1c : 5.7 – 6.4



e. Prognosis :

- ☒ IGT (impaired glucose tolerance) leads to type 2 DM in about 34% of cases over 5 years.
- ☒ IGT & IGF together : lead to type2 DM in 65% of cases.
- ☒ Prediabetics are at high risk for cardiovascular complications.

f. This group includes :

- i. +ve family history.
- ii. Obesity.
- iii. ♀ with bad obstetric history → macrosomia.
- iv. Renal glucosuria.

II. Latent diabetes :

Diabetes appears only on exposure to stress & disappears after removal of stress e.g. pregnancy.

III. Chemical diabetes : Raised blood glucose with no symptoms.

IV. Clinical diabetes :

a. Uncomplicated : Classic triad of symptoms : **3 p**

- **polyuria** : due to osmotic diuresis induced by sugar.
- **polydipsia** : due to loss of fluid.
- **polyphagia with weight loss** : ↓ insulin → no glucose can enter satiety center → ↑↑ of satiety center. While loss of weight is caused by fluid depletion , fat & muscle breakdown.

b. Complicated : May be the 1st presentation. see later

Investigations of DM :

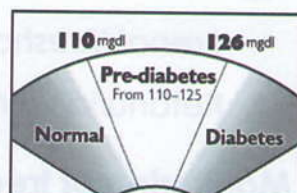


I. Blood :

1. Blood sugar tests :

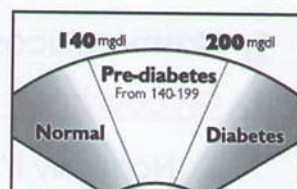
i. Fasting blood glucose : (no caloric intake for at least 8 hours)

- 70 - 110 mg % $\rightarrow$ normal.
- ≥ 126 mg % (≥ 7.0 mmol/l) $\rightarrow$ DM.
- 110 - 125 mg % (6.1 - < 7.0 mmol/l) $\rightarrow$ Impaired fasting glucose (IFG)



ii. 2 h. post-prandial :

- < 140 mg % $\rightarrow$ normal.
- ≥ 200 mg % (11.1 mmol/l) $\rightarrow$ DM.
- 140 - 199 mg % $\rightarrow$ Impaired glucose tolerance (IGT)



- To convert mmol/l of glucose to mg/dl, multiply by 18. (... X 18)
- To convert mg/dl of glucose to mmol/l, divide by 18 or multiply by 0.055.

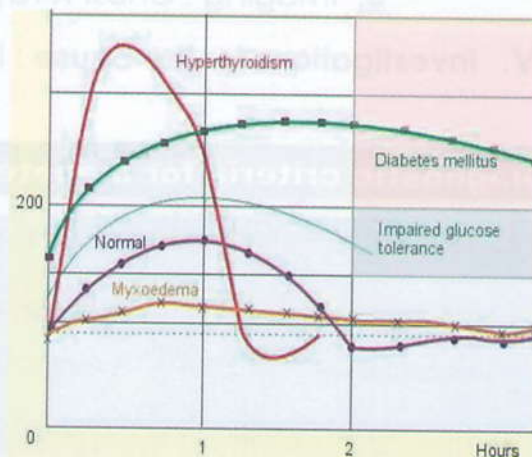


2. Oral glucose tolerance test : (OGTT)

- Patient should be fasting over night.
- Fasting blood sugar is done.
- The patient drinks a glucose solution containing 75 g glucose within four minutes (WHO).
- Take blood samples every 1/2 h. for 2 - 3 h.

v. Normal curve : 3 criteria

- 1) Fasting : 70-110 mg %
- 2) Reach maximal point in 1h. but still under 180 mg %
- 3) Return to normal within 2 h.



3. Cortisone glucose tolerance test :

- i. Dexamethazone 3 mg is given before OGTT.
- ii. It will induce hyperglycemia in latent & pre diabetes.

II. Urine :

1. Glucosuria : occurs when glucose serum level exceeds 180 mg % (renal threshold); but it's not a good indicator for DM diagnosis.
2. Ketonuria : for diagnosis of diabetic ketoacidosis.

III. Monitoring of treatment :

1. Plasma glucose monitoring.
2. Glycosylated hemoglobin (HBA_{1c})
 - i. Normally it's less than 5.5 % of total HB.
 - ii. A_{1c} ≥ 6.5 in DM. (prediabetes : 5.7 – 6.4)
 - iii. $> 12\%$ $\rightarrow$ poor glycemic control in the past 3 months.

IV. Investigations for complication :

1. Plasma lipids.
2. Renal : Urine analysis, serum creatinine, electrolytes.
3. Imaging : Chest X-ray, ECG, echo, duplex carotid & LL

V. Investigations for the cause : If 2ry diabetes is suspected

Diagnostic criteria for diabetes : (American Diabetes Association)

1. A glycated hemoglobin level $\geq 6.5\%$
2. Fasting plasma glucose of 126mg/dL (7 mmol/L) or greater on TWO separate occasions.
3. Classic symptoms of hyperglycemia (e.g. 3 Ps) **PLUS** random glucose of > 200 mg/dL.
4. 2 hours postprandial glucose of 200 mg/dL (11.1 mmol/L) or greater confirm the presence of diabetes.

Pathogenesis of diabetic complications :

1. **Recurrent infections** : *not only common but are often more severe*

It is due to impaired PMN functions (particular when acidosis is present) :

- Impaired Leukocyte migration & phagocytosis.
- Decrease of antioxidant activities.
- Acidosis can inhibit antibodies production.

2. **Glycosylation of blood vessels** :

This may lead to thickness of basement membrane of capillaries with narrowing of their lumen, leading to vasculopathy (**Micro** & macro angiopathy)

3. **Biochemical (accumulation of sorbitol)** :

Glucose is reduced to sorbitol by aldose reductase → ↓ of ATPase activity → leading to neuropathy & nephropathy.

Complications of DM

Cutaneous :

1. **Infections** :

- Carbuncles & recurrent abscesses.
- Fungal infections : *especially in the ano-genital region & interdigitals.*

2. **Pruritis** : *especially pruritis vulvae due to monilial infection.*

3. Delayed healing of the wounds.

4. **Xanthelasma** ; *due to hyperlipidemia.*

5. **Necrobiosis lipoidica diabetorum** :

- Red **painless papules** with yellow center.
- Site : Usually over the anterior surface of the legs.
- Cause : cutaneous blood vessels occlusion.

6. Cutaneous features of diabetic foot.

7. **Acanthosis nigricans** : black patches due to insulin spillover into the skin in type 2 DM (*excess insulin*). **MCQ**

8. Lipodystrophy : at the sites of insulin injection.

Cardiovascular :

1. **Microangiopathy** : (*Microvascular complications*)

- a) Diabetic retinopathy → retina.
- b) Diabetic nephropathy → glomeruli.
- c) Diabetic neuropathy → vasa nervosa.

2. **Macroangiopathy** : (*Atherosclerosis*)

- a) Cerebral : thrombosis & ischemia.
- b) Coronary : angina & MI, may be painless due to neuropathy
- c) Peripheral : gangrene & intermittent claudication.
- d) Renal : reno-vascular hypertension.

3. **Cardiomyopathy** : due to microangiopathy.

4. **Blood pressure** :

- a) systemic hypertension.
- b) postural hypotension due to autonomic neuropathy.

Causes of HTN in diabetic patient :

- 1- Diabetic nephropathy.
- 2- Endothelial dysfunction.
- 3- Insulin → retention of Na.
- 4- 2ry diabetes : Cushing & acromegaly.
- 5- Type 2 DM may be a part of **metabolic syndrome X** which consists of :
(DM, hypertension, Hyperlipidemia, obesity).

Chest :

- 1. **Recurrent chest infection** e.g. T.B. (***T.B. follows DM as its shadow***).
- 2. **Rapid deep respiration** Kussmaul respiration & acetone smell in DKA.

Gastrointestinal : Diabetics never have normal bowel habits

1. Mouth : gingivitis , loosening of teeth.

2. Stomach :

- Gastroparesis .
- Nausea, vomiting & abdominal pain in DKA.

3. Intestine :

○ Diarrhea due to : ABCD

- ✓ Autonomic neuropathy.
- ✓ Bacterial overgrowth.
- ✓ Celiac disease (autoimmune).
- ✓ Drugs : e.g. metformin, incretins.

○ Constipation : due to vagal neuropathy.

4. Liver : fatty liver (NAFLD)

5. Gall bladder : chronic cholecystitis , gall stones.

Genital :

1. In ♂ : Impotence (psychological, neuropathy, vasculopathy)

2. In ♀ : Infections & pruritis vulvae.

3. Effects of DM on pregnancy :

- On mother :

- i. Eclampsia.
- ii. Post Partum hemorrhage.
- iii. Puerperal sepsis.

- On fetus :

- iv. High birth weight.
- v. Hypoglycemic baby.
- vi. Congenital anomalies.

4. Effects of pregnancy on DM :

- i. ↑ needs for insulin due to ↑ anti-insulin : estrogen.
- ii. ↓ renal threshold for glucose.
- iii. ↑ incidence of complications.

Eye :

1. **Lids** : Infections (chalazion , conjunctivitis) , Xanthelasma.

2. **Iris** : New vessels formation in iris (rubeosis iridis)

3. **Lens** :

- Senile cataract (occur at an earlier age)
- Repeated error of refraction secondary to osmotic lens changes with fluctuating glucose level : Hyperglycemia leads to myopia, Hypoglycemia leads to hypermetropia.

4. **Nerves** : Optic neuritis , Cranial nerve palsy (3, 4 & 6 nerves).

5. Diabetic retinopathy :

- a. It's the most characteristic form of diabetic eye diseases.
- b. It is related to the duration & control of the disease.
- c. It eventually occurs in nearly all patients of type 1 DM 10 years after diagnosis. It is present in 10% of type 2 DM at diagnosis, 50% after 10 years and 80 % after 20 years.
- d. It is usually accompanied by nephropathy & neuropathy.
- e. Detected by *fluorescein angiography*.
- f. There are 2 important types :

- **Non proliferative (background retinopathy)** :

- ✓ Characterized by ↑ capillary permeability, **Microaneurysms**, hemorrhage , exudates. **MCQ**
- ✓ During this stage of diabetic retinopathy, no local treatment required , except in a case of **diabetic maculopathy**, just good control of diabetes and hypertension and stopping smoking.

- Proliferative :

Characterized by neovascularization, retinal detachment. this type must be treated as early as possible by laser photocoagulation.

☛ without treatment 50% of proliferative patients become blind within 5 – 10 years.

- Proliferative retinopathy : more common in type 1 DM.
- Diabetic maculopathy : more common in type 2 DM.

Renal :**1. Interstitial injury :**

- Pyelonephritis : ▪ Fever ▪ Pain. ▪ Dysuria. ☛
- Acute necrotizing papillitis : fever , pain , dysuria and hematuria.

2. Diabetic nephropathy : (Diabetic glomerulosclerosis)**Definition :**

Clinical syndrome characterized by ↑ in urine albumin excretion , ↑ BP up to end stage renal failure with progressive rise in CV risk.

Incidence :

- Long standing DM (30% of type1 , 20 % of type2) .
- Genetic factor may play a role.

Pathogenesis : Glomerular sclerosis :

- i. Early Thickening of basement membrane of glomeruli & mesangial expansion .
- ii. Hyalinization of afferent & efferent arterioles.

Glomerular hyperfiltration ⇒ proteinuria ⇒ end stage renal disease.

DM affects efferent more than afferent arterioles . So ; there is more narrowing in efferent than in afferent, this ↑↑ intra-glomerular pressure ⇒ this will allow plasma proteins to escape into the urine
⇒ Some of these proteins will be taken up by the proximal tubular cells, which can initiate an inflammatory response that contributes to interstitial scarring eventually leading to fibrosis.

Types :

- i. Nodular (Kimmelestiel-Wilson's syndrome)
- ii. Diffuse.

Clinical picture :

- i. Long standing DM especially poorly controlled diabetes after about 10-20 years. (rarely develops before 10y duration of the disease)
- ii. Proteinurea : **the early clinical sign of diabetic nephropathy**
 1. micro-albuminuria : 30-300 mg/day It is reversible by **ACEIs** .
 2. macro-proteinuria : > 300 mg/day
 3. heavy proteinurea (nephrotic syndrome)

Nearly 100% with gross proteinuria will progress to End Stage CRF in 5 – 15 y ☹
- iii. Lately, progressive loss of renal function (**CRF**) .
- iv. Hypertension, diabetic retinopathy & neuropathy are usually present.

In patient with type1 DM, nephropathy **almost always** occurs in the **presence of retinopathy**

Show me your intelligence : 😊

Mamdouh, 21 year old male with type 1 DM, 4 years ago comes for follow up. He has noted that his urine is foamy but otherwise has no complaint. Eye examination shows no retinopathy. Urine analysis shows 4+ proteinuria. The most likely cause of proteinuria in this patient is :

- a) Diabetic nephropathy
- b) **Membranous GN**
- c) Minimal change disease
- d) Post streptococcal GN

WHY ??

This case is **NOT** diabetic nephropathy. The absence of eye disease as seen in our patient should prompt consideration of other causes of nephropathy. As membranous GN is the most common cause of nephritic syndrome in adult, answer b is the correct answer.

Stages of diabetic nephropathy :

A) Incipient nephropathy :

- **Stage I :** Nephromegally , $\uparrow$ GFR.
- **Stage II :** Stage I + microalbuminuria on exercise.
- **Stage III :** as stage 2 but persistent microalbuminuria > 30 mg/d.

This stage may remain silent for up to 10 – 15 years.

B) Overt nephropathy :

- **Stage IV :**
 - ✓ Macro proteinuria > 300 mg/d . (rarely the proteinuria exceed 5 gm /d)
 - ✓ $\downarrow$ GFR.
 - ✓ Hypertension is common.
- **Stage V :** End stage CRF.

Investigation :

1- Urinalysis : **Screening of microalbuminuria** is a mandatory .

It should be performed in type 1 patients who have had diabetes > 5 years and all type 2 diabetic patients starting at diagnosis (In type 2 DM , microalbuminuria can be present at the time of diagnosis).

2- Blood : urea & creatinine.

3- U/S : **Normal** sized kidneys with $\uparrow$ echogenicity. (not shrunken as usual CRF)

4- Biopsy : may be done if there is any doubt in the diagnosis. It is not always necessary if the case is straightforward, with a documented progression of proteinuria over time and presence of diabetic retinopathy.

Treatment :

- 1- Diabetic control can reverse the microalbuminuria.
- 2- Control of hypertension is a mandatory by **ACEIs & ARBs** which decrease the albuminuria even in normotensive patients.
- 3- Treatment of CRF : **3D + T** see nephrology book

Diabetic foot :

Definition :

The foot of a diabetic patient that has the potential risk of pathologic consequences, including infection, ulceration.

Pathogenesis :



Neuropathy, vasculopathy, & infection combine to produce tissue necrosis.

1) Neuropathy :

- a. Sensory neuropathy → ↓ awareness of injury to the foot.
- b. Motor neuropathy → Abnormal motor function of the intrinsic muscles of the foot → foot deformity → maldistribution of weight.
- c. Autonomic neuropathy → ↓ sweating → dry & fissured skin → infection.

- In severe cases the abnormal distribution of weight on the sole can result in repeated painless fractures and displacement of joints producing the so-called *Charcot joints*.

- **Charcot joint** : (*neuro-arthropathy*) : Non-infectious destruction of bone & joint associated with neuropathy.

2) Vasculopathy : (*Impaired peripheral circulation*)

Ischemia will affect the ability to fight infections since delivery of antibiotics to the site of infection will be impaired.

3) Infection :

- Diabetic foot infections are polymicrobial in nature.
- Lack of wound healing, systemic sepsis, neuropathy & vasculopathy can lead to extensive tissue necrosis and gangrene requiring amputation to prevent more proximal limb loss.

Clinical features of diabetic feet :**- Site of ulceration : at pressure points e.g.**

- Base of the big toe (head of the first metatarsal bone)
- Base of the 5th metatarsal.
- Heel.

- Neuropathic & Ischemic feet :

Neuropathic feet	Ischemic feet
- Warm - Dry - Foot pulses felt - Usually painless ulcer - Callus present	- Cold - Trophic changes/ hairless - Foot pulses not felt - More often painful - Rest pain & claudication.

Wagner's classification of diabetic foot lesions :

Grade 0	High risk foot-no ulceration.
Grade 1	Shallow ulcer-not infected.
Grade 2	Deep ulcer with cellulites but no abscess or bone involvement.
Grade 3	Deep ulcer with bone involvement or abscess formation.
Grade 4	Localised gangrene (toes, heel).
Grade 5	Gangrene of whole foot.

Risk factors for foot ulcers or amputation include :

5 Ps

- ☠ **P**oor glycemic control & Diabetes for > 10 years.
- ☠ **P**eripheral neuropathy.
- ☠ **B**ony abnormalities & callus.
- ☠ **P**eripheral vascular disease.
- ☠ **P**revious foot trauma or surgery.

Treatment :**I. Prevention of foot ulcers : 6 Ps**

1. **P**odiatric care (footcare) : regular visits, examinations.
2. **P**atient education : control of diabetes, foot cleaning, careful nail cutting.
3. **P**ulse examination.

4. **Protective shoes** : avoid bare foot & tight shoes.
5. **Pressure reduction** : Crutches, Cushioned insoles, foot cast.
6. **Prophylactic surgery** : to reduce bony prominence.

II. Treatment of diabetic foot infections :

1. Wound care e.g. dressing.
2. Empiric antibiotic coverage, modified by culture findings.
3. Debridement of necrotic tissue.
4. Angioplasty to improve the distal circulation.
5. Amputation may be necessary in extensive cases.



Diabetic foot ulcer



Ischemic gangrene



Charcot foot

Diabetic infections :

1. Skin : Staph & candida .
2. Urinary tract : Pyelonephritis & perinephric abscess.
3. Chest : T.B. & pneumonia.
4. Genital : Pruritis vulva.
5. GB : Cholecystitis.

6- Life threatening infections in diabetics :

☠ Malignant otitis externa :

- It is an uncommon but potentially life-threatening infection, almost always due to *Pseudomonas aeruginosa*.
- Patients report a history of weeks to months of severe pain, otorrhea, and hearing loss. Intense cellulitis is combined with edema of the ear canal.
- CT and MRI studies are essential for defining the extent of bone and soft-tissue involvement.

☠ Rhino-cerebral mucormycosis :

- Mucormycosis is a life-threatening fungal infection.
- Patients present with facial or ocular pain and nasal obstruction followed by proptosis and loss of visual acuity. Generalized malaise and fever, necrotic turbinates may be found.
- Treatment consists of surgical debridement of the involved sinuses and prolonged intravenous therapy with amphotericin B.

☠ Emphysematous cholecystitis :

- It is a severe form of acute cholecystitis characterized by gas production in the gallbladder wall. *Clostridium* spp. are often isolated from bile cultures in addition to other enteric flora.
- It is frequently associated with gangrene, perforation, and death.
- Diagnosis involves the demonstration of gas within the lumen or walls of the gall bladder by ultrasound or CT scan.
- Surgical intervention is necessary in addition to broad-spectrum antibiotics.

Neurological :

- I. **Diabetic macroangiopathy**
- II. **Diabetic neuropathy.**
- III. **Diabetic comas.**

I. **Diabetic macroangiopathy** : (due to atherosclerosis)

- a. Cerebral hemorrhage.
- b. Cerebral thrombosis.

II. **Diabetic neuropathy** :

Pathogenesis : unknown but there are 4 important theories :

1. Hypovitaminosis : polyuria washes water soluble B complex.
2. Microangiopathy of vasa nervosa.
3. Metabolic ketosis : toxic effect of keton bodies.
4. Transformation of glucose to sorbitol by aldose reductase enzyme.

C/P : (may precede the discovery of DM)

1. **Mononeuropathy or mononeuropathy multiplex, affecting** :

- a. Peripheral nerves : femoral , ulnar & median nerves.
- b. Cranial nerves : 3 , 4 , 6 . MCQ

2. **Polyneuropathy** :

- a. Sensory affection is more than motor affection.
- b. Superficial sensation : Symmetrical parasthesia especially in LL followed by stock & glove hyposthesia.
- c. Deep sensations : nocturnal calf spasm is common.
- d. Motor weakness is late.

3. **Autonomic neuropathy** :

- CVS :

- Postural hypotension.
- Painless myocardial infarction.
- Persistent tachycardia .

- GIT :

- Gastroparesis : delayed gastric emptying.
- Diarrhea : severe, nocturnal & alternating with constipation.

- Genito-urinary :

- Impotence.
- Incontinence.

- Skin :

- Generalized sweating.
- Edema of the feet due to loss of the vasomotor tone.
- Trophic ulcers.

Treatment :

- Strict control of DM : diet, oral hypoglycemic or insulin.
- Reassurance may be all that needed.
- Physiotherapy if motor weakness is present.
- **Drugs :** *Low benefit*
 - a. Analgesics of neurotic pain : carbamazepine (Tegretol)
 - b. Vit. B complex (Tri B) & ATP (adenoplex).
 - c. Aldose reductase inhibitors : sorbinil.
 - d. Cerebrolysin. (nerve growth factor)

III. Diabetic comas : (Acute diabetic complications)

1. Hypoglycemic coma. (insulin reaction) : The most common
2. Diabetic ketoacidosis. (DKA)
3. Hyperglycemic hyperosmolar non ketotic coma.
4. Diabetic lactic acidosis.
5. Other causes of coma : uremic, hepatic,

Hypoglycemic coma

a. Etiology :

- Missed meal or severe exercise after insulin or oral hypoglycemic drugs.
- Over dose of insulin or decreased elimination of insulin as in cases of renal failure.

b. C/P : severity of symptoms can vary with the individual.

i. **Adrenergic symptoms** : (warning signs)

due to ↑ catecholamines when blood glucose < 50 mg %

- 1- Tachycardia (palpitation).
- 2- Sweating.
- 3- Tremors.
- 4- Anxiety.
- 5- Hunger pain.

ii. **CNS symptoms** :

due to cerebral dysfunction when blood glucose < 30 mg %

- 1- Headache.
- 2- Blurring of vision.
- 3- Lack of concentration.
- 4- Convulsion may occur.
- 5- Coma.

Masked symptoms of hypoglycemia may occur in the following conditions : (not associated with adrenergic symptoms)

- During night.
- β -blockers.
- Old age.
- Recurrent hypoglycemia.

c. **Investigation** : Low blood glucose < 50 mg % in male & 45 % in female.

d. **Differential diagnosis** :

- From diabetic ketoacidosis : see later.
- From other causes of hypoglycemia : see later.

e. **Treatment** : Recovery is very rapid except in irreversible brain damage

- i. If patient is conscious : oral glucose in the form of candy.
- ii. If there is coma : IV glucose 50 gm 50 % .
- iii. Hypoglycemia due to oral hypoglycemic drugs (sulphonylurea) : may persist for long time (days) so glucose has to be infused for long time.

Diabetic ketoacidosis “DKA”

a. **Definition** :

DKA is an extremely serious metabolic complication of DM due to **sever** insulin deficiency, it's characterized by triad of : 🖐

- Acidosis. - Ketosis. - Hyperglycemia (usually >250 mg %).

NB : *There is no relation between the severity of hyperglycemia & the severity of ketoacidosis.*

b. **Etiology** : ket**ONE** bodies are seen in type **ONE** DM ☺

- Occurs mainly in type 1 DM, due to sever insulin deficiency e.g.
 - Previously un diagnosed DM
 - Missed insulin (neglected treatment).
- **Precipitating factors** :
 - **I**nfections (lead to increased insulin requirements).
 - **I**nfarction (I mean myocardial infarction).
 - **I**ntoxication (Alcohol).

In type 1 DM : DKA occurs with or without Precipitating factors.

In type 2 DM : DKA occurs with Precipitating factors only.

Diagnosis of infection in DKA may be difficult because :

- ✎ Firstly, The temperature in patients with DKA is subnormal so the absence of fever is not enough to exclude infection.
- ✎ Secondly, leucocytosis occurs in DKA in the absence of infection.

c. Pathogenesis & C/P : sever insulin deficiency leads to : ✎

- i. **Glucose can't enter the cells** → hyperglycemia > 250 mg %.
- ii. **Fat : ↑↑ lipolysis** to produce energy → ↑ production of keton bodies (β -hydroxy buteric acid, acetoacetic acid & acetone) → ketoacidosis (PH < 7.3)
- iii. **Effects of ketoacidosis :** gradual onset of : ✎ X 2
 - 1- **Muscles :**
 - a. Generalized weakness.
 - b. Muscle pain.
 - 2- **Kidney :** ketonuria together with glucosuria lead to sever
 - a. Polyuria.
 - b. Dehydration.
 - 3- **GIT :**
 - a. Anorexia, nausea & vomiting.
 - b. **abdominal pain.**
 - 4- **Respiration :**
 - a. Kussmaul respiration (deep rapid)
 - b. Acetone odor of breath.
 - 5- **CVS :**
 - a. Depressed contractility & low blood pressure.
 - b. Rapid weak pulse.
- iv. **Hyperkalemia** due to shift of K outside cells in absence of insulin.
- v. **Coma** due to combined effect of : Ketone bodies, dehydration & electrolyte disturbance.

d. Investigations :**i. Blood examination :**

- $\uparrow$ glucose > 250 mg %, $\uparrow$ ketone bodies.
- Acidosis (PH < 7.3) with high anion gap.
- Electrolytes : $\uparrow\uparrow$ K . Hypokalemia may occur due to polyuria

ii. Urine examination : Polyuria, glucosuria & ketonuria.**e. Treatment :**

Estimation of blood glucose, PH, blood gases & electrolytes (K, Na)

i. Fluid therapy :

- 4-8L is usually required.
- Normal saline 1 L/hour for the first 2 h followed by $\frac{1}{2}$ L/h until the deficit is replaced. 4-8 L is usually required.
- At first hour, normal saline is given, then change to glucose 5% saline if blood glucose becomes < 250 mg/dl.

ii. Insulin :

- Short acting soluble insulin (regular, *crystalline insulin*).
- **Regimen : IV or IM**
 - ✓ IV insulin infusion : 5 – 10 u/ h infusion.
 - ✓ Repeated IM : 20 U at the start then 6 U/ h
 - ✓ SC route is ineffective because of hypotension & reduction of skin blood flow.
- **First hour :** 5 – 10 U/h IV infusion
- **Second hour :**
 - ✓ Continue insulin 5-10 U/h IV infusion as long as acidosis is present.
 - ✓ If blood glucose does not decrease by 10% after the first hour the insulin dose is increased.

✓ If blood glucose becomes below 250 mg/dl, add glucose 5% IV infusion.

- **Third hour** : continue insulin IV infusion till PH becomes > 7.3 , $\text{HCO}_3^- > 18$, AG becomes normal, then give SC regular insulin before meals.

iii. **K therapy** :

The serum K falls during insulin therapy (*intracellular shift*), and this fall may be dramatic. so add (20 – 40 mEq) to each 1L saline.

iv. **Na bicarbonate** : in sever acidosis [PH < 6.9]

v. **Treatment of precipitating factors** e.g. infection : antibiotics.

Complications during the treatment of DKA :

- Hypoglycemia.
- Hypokalemia.
- Hypervolemia.
- Rebound cerebral edema : it occurs in children & young adult if plasma glucose is decreased rapidly → shift of water to the cells → brain edema. This can be prevented by gradual reduction of plasma glucose (75 mg/h)

	Hypoglycemic coma	DKA
▪ History :	- Missed meal.	- Missed insulin.
▪ Onset :	- Acute.	- Gradual.
▪ Pulse :	- Strong .	- Weak & rapid.
▪ BL.P. :	- ↑	- ↓
▪ Skin :	- Sweaty.	- Dry .
▪ Pupils :	- Dilated.	- Normal.
▪ Respiration :	- Normal.	- Rapid , deep.
▪ Urine :	- Normal.	- +ve sugar & acetone.
▪ Coma :	- Irritable.	- Not irritable.
▪ IV glucose :	- Rapid recovery.	- No effect.

Hyperglycemic hyperosmolar non ketotic coma (HHNK)

- There is low insulin level which is enough to prevent ketosis , but not enough to inhibit hyperglycemia, so there is hyperglycemia without ketosis.
- It occurs in old type 2 DM.
- Patients typically having sever hyperglycemia (> 600 mg/dl), sever dehydration. Plasma osmolality > 340 mOsm/L (N : 290) is the landmark of this condition.
- **Clinical picture :**
 - Sever hyperglycemia : polyuria , polydipsia.
 - Sever dehydration $\Rightarrow$ renal failure & thrombotic complications.
 - Sever hyperosmolality $\Rightarrow$ CNS symptoms (convulsions , coma).
- **Treatment :** The same as DKA but
 - Aggressive fluid replacement. (**the most important measure**)
 - Low rate of Insulin infusion (3 U/h).
 - S.C. heparin to prevent thrombotic complications.
 - Na bicarbonate is not given.

Lactic acidosis

- It occurs in diabetics using high dose of biguanides e.g. *metformin*
- Biguanides $\Rightarrow$ tissue hypoxia $\Rightarrow$ anaerobic glycolysis $\Rightarrow$ accumulation of lactic acid.
- **C/P :**
 - a. Rapid deep respiration (Kussmaull respiration).
 - b. Confusion , coma.
- **Treatment :** NaHCO_3

DIAGNOSTIC CRITERIA OF DIABETIC COMAS

DKA	HHNK	Lactic acidosis
○ Hyperglycemia > 250 mg/dL. ○ Acidosis with blood PH < 7.3 with high anion gap. ○ Serum bicarbonate < 15 mEq/L ○ Serum positive for ketones.	○ Hyperglycemia > 600 mg/dL. ○ Serum osmolality > 310 mosm/kg. ○ No acidosis, blood PH > 7.3 ○ Serum bicarbonate > 15 mEq/L.	○ Severe acidosis with hyperventilation. ○ Acidosis with blood PH < 7.3 with high anion gap. ○ Serum bicarbonate < 15 mEq/L ○ Absent serum ketone. ○ Serum lactate > 5 mmol/L.

- **Acute diabetic complications : diabetic coma.**
- **Micro-vascular complications : diabetic triopathy.**
- **Hyperglycemic coma : DKA , HHNK.**

Treatment of DM :

- I. General measures.
- II. Diet.
- III. Oral hypoglycemic.
- IV. Insulin.
- V. Treatment of complications.

I. General measures :

- a. Reassurance.
- b. Education about nutrition & lifestyle modifications.
- c. Exercise.

II. Diet :

- a. It's an **important** item in control of DM
- b. Diet alone can control mild cases of type II DM
- c. **Total calories/day :** *depending on weight & physical activity*
 - i. Mild activity → 1500 cal/d.
 - ii. Moderate activity → 2500 cal/d.
 - iii. Severe activity & pregnancy → 3500 cal/d.

d. **Food components :**

- i. CHO : 50% of calories . avoid simple sugars.
- ii. Fat : 30% of calories . avoid saturated fat.
- iii. Protein : 20% of calories.
- iv. Vitamins : B-complex & vit. A
- v. ↑↑ fibers : ↑ satiety.

e. **Number of meals :**

3 main meals + 2 snacks in between, to avoid hyperglycemia or hypoglycemia.

III. Oral hypoglycemic drugs

a. Biguanides :

- **Mechanisms of action :**

- 1. ↑ anaerobic glycolysis.
- 2. ↓↓ intestinal glucose absorption.
- 3. ↓↓ appetite.

- **Preparations :** Metformin (*Cidophage*) 500 - 850 mg t.d.s.

- **Indications :**

- 1. type 2 DM not controlled by diet alone esp. in obese patients.
- 2. combined with sulphonylurea or insulin to achieve control.

- Side effects :

- ☠ Contraindicated in renal failure (discontinue usage if creatinine ≥ 1.5)
- ☠ Nausea, vomiting, diarrhea, and abdominal upset.
- ☠ Lactic acidosis.

b. Sulphonylureas :**- Mechanisms of action :**

1. $\uparrow\uparrow$ insulin secretion from pancreas. (main action)
2. $\uparrow\uparrow$ peripheral action of insulin (insulin sensitizer)
3. $\downarrow\downarrow$ hepatic production of glucose.

- Preparations :

Drug	Trade name	Dose (mg/d)	Duration of action
▪ Old generation :			
- Chlorpropamide	<i>Pamidine</i>	100 - 500	long acting
- Tolbutamide	<i>Diamol</i>	500 - 3000	short
▪ New generation :			
- Glibenclamide	<i>Doanil.</i>	2.5 - 15	long acting
- Glimepiride	Amaryl.	1 - 6	long acting
- Gliclazide	Diamicron.	80 - 480	intermediate
- Glipizide	<i>Minidiab</i>	2.5 - 30	short

- Indication :

Type 2 DM not controlled by diet alone especially in non obese patients.

- Side effects :

- Allergy.
- Aplastic anemia.
- Hypoglycemia.
- Hepatitis.
- Hyponatremia due to increased ADH by chlorpropamide.

MCQ

c. Recent drugs :**1- Alpha glucosidase inhibitors : Acarbose (*glucobay*)**

- Prevent breakdown of CHO in intestine → ↓ glucose absorption.
- Disadvantage : Contraindicated in hepatic patient , abdominal pain.

2- Glinides : Repaglinide , Nateglinide.

- Stimulate secretion of insulin from beta cells.
- Rapid onset & short duration , acts on post prandial hyperglycemia.

3- Thiazolidinediones : (*Rosiglitazone*)**MCQ**

- Increases insulin sensitivity
- Can be combined with sulfonylurea, metformin or insulin.
- Advantage : improve diabetic dyslipidemia.
- Disadvantages :
 - ✓ Contraindicated in mild liver impairment.
 - ✓ Given cautiously to patient with heart failure, renal impairment.
 - ✓ Weight gain , mild edema.

All oral hypoglycemic drugs are given cautiously to patient with hepatic, renal & heart failure.

4- Incretins : ***

- Incretins are hormones that are released from the gut into the blood within minutes after eating. Incretin hormones are insulintropic (they induce insulin secretion after eating).
- **There are two incretins :**
 - a) **Glucose-dependent insulintropic peptide (GIP) :** It is released from K cells in the duodenum and jejunum.
 - b) **Glucagon-like peptide-1 (GLP-1) :** from L cells small intestine & ascending colon.
- Both incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase 4 (DPP4).

- Since 2005, two new classes of drugs based on incretin action have been approved for lowering blood glucose levels in type 2 DM :

I. Incretin mimetic (exenatide) :

- Exenatide is injected subcutaneously twice daily, 1h prior to meal
- It used in combination with metformin or sulfonylureas.

II. Dipeptidyl peptidase IV inhibitors (gliptins) :

e.g. Sitagliptin – Saxagliptin – Vildagliptin

- DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the incretin hormone.
- The DPP4 inhibitors have an advantage in that they are effective when administered orally, but they do not have as potent effect as exenatide.

- **Mode of action of incretins** : increase postprandial active incretins (GLP-1 & GIP), which in turn decrease blood glucose level by :

- Increasing insulin secretion.
- Decreasing glucagon.
- Decreasing gastric emptying.

○ Advantages :

- No hypoglycemia, no weight gain, well tolerated.
- HbA1c reduction of 1% and seems to improve β -cell function.

○ Side effects :

- Nausea, vomiting & diarrhea.
- Pancreatitis.

IV. Insulin

- Human insulin is a peptide hormone composed of 51 amino acids. It is synthesized in the pancreas within the β -cells of the islets of Langerhans.
- A typical blood level between meals is 8–11 $\mu\text{IU/ml}$. **MCQ**

- Action :

i. Rapid action :

Insulin stimulates **2** things to go Into the cells : glucose & K ☺

ii. Gradual action :

1. CHO : hypoglycemia

a. $\uparrow$ glycogenesis. b. $\downarrow$ gluconeogenesis.

c. $\uparrow$ peripheral utilization of glucose.

2. fat : - $\uparrow\uparrow$ lipogenesis. - $\downarrow\downarrow$ lipolysis.

3. protein : anabolic.

- Preparations : was discovered in 1921.

Type	Trade names	Duration of action
1- Short-acting : (soluble)	- Neutral (regular). - Humulin R - Semilente.	Onset : $< \frac{1}{2}$ h. Peak : 2 – 4 h. Duration : 6 – 8 h.
2- Intermediate :	- Isophane (NPH) - Humulin N - Lente.	Onset : 2 h. Peak : 6 – 8 h. Duration : 12 – 24 h.
3- Long-acting :	- Protamine zinc insulin - Humulin L - Ultralente	Onset : 6 – 8 h. Peak : 12 – 24 h. Duration : up to 36 h.
4- Insulin mixture :	30% short + 70% NPH (mixtard)	

- Indications :

- i. All type 1 DM.
- ii. Type 2 DM not controlled with diet & oral hypoglycemic.
- iii. During pregnancy, infection & surgery.
- iv. DKA & HHNK .

- v. $\uparrow\uparrow K$ (Hyperkalemia).
- vi. Insulin stimulation test in pan-hypopituitarism.

- **Dose : trial & error** (s. c. , 1 cm mixtard = 40 u)

- i. Start with 20 – 30 U / d (20 U in non obese , 30 U in obese patient)
- ii. The dose is gradually $\uparrow$ (by 5 u / d) until blood glucose is controlled.
- iii. $\frac{2}{3}$ of dose before breakfast & $\frac{1}{3}$ of dose before lunch.
- iv. $\frac{2}{3}$ of dose intermediate & $\frac{1}{3}$ of dose short acting insulin (**mixtard**)

- If mixtard is not available $\rightarrow \frac{1}{3}$ regular insulin + $\frac{2}{3}$ NPH can be mixed in the syringe & injected as rapid as you can.

- **Multiple SC insulin injection (MSII)** : in cases of poor glycemic control

- o 75% of the dose is given as regular insulin before each meal.
- o 25 % of the dose is given as intermediate insulin before sleep.

- **Administration :**

- i. S.C.
- ii. Insulin pump (**C**ontinuous **S**.C Insulin Infusion , CSII) .
- iii. IV infusion or IM : in case of DKA , HHNK
- iv. Insulin pens.
- v. Oral , nasal & rectal insulin $\rightarrow$ under trial ?

- **Side effects :**

- i. Hypoglycemia & hypoglycemic coma.
- ii. Allergy : use human insulin.
- iii. Insulin resistance :
 - o obesity $\rightarrow$ mild resistance.
 - o antibodies against insulin.
- iv. Insulin lipodystrophy : atrophy or hypertrophy of s.c. fat at the site of insulin injections.

- v. Insulin edema : Na & H₂O retention ⇒ Hypertension.
- vi. Weight gain.
- vii. Pseudo insulin resistance (*Somogi effect*) : nocturnal hypoglycemia due to over insulin dose at night → ↑↑ anti-insulin hormones → rebound hyperglycemia in the morning. This condition is treated by reduction of the evening insulin dose.

MCQ

- Pramlintide : “amylinomimetics”

- Is synthetic amylin analogue.
- Used in type 1 or insulin requiring type 2 DM.
- Given with current diabetic regimen.
- Mode of action : Pramlintide injected SC just before a meal slows gastric emptying & suppresses glucagon but doesn't alter insulin levels.
- S/E : nausea , vomiting , frequent dosing injection (3 times daily)



V. TTT of the complications.

Q : criteria for good diabetic control ?

▪ Lab. :

- Fasting plasma glucose (90 - 130) mg/dl
- Post prandial plasma glucose : < 180 mg/dl.
- HbA_{1c} < 7%.

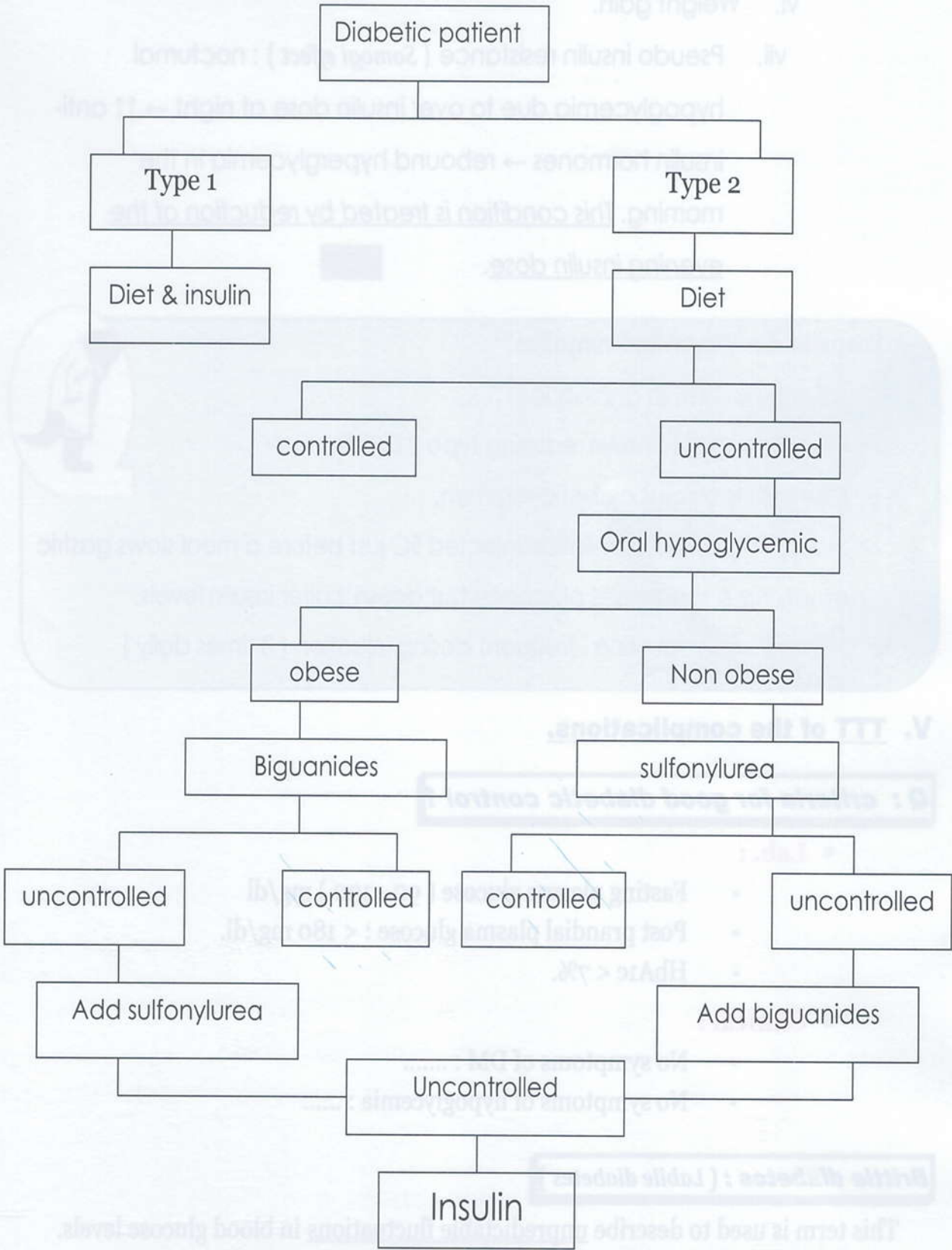
▪ Clinical :

- No symptoms of DM :
- No symptoms of hypoglycemia :

Brittle diabetes : (Labile diabetes)

This term is used to describe unpredictable fluctuations in blood glucose levels. These cause either recurrent hypoglycemia or hyperglycemia.

Scheme for treatment of DM :



Hypoglycemia

Causes :

I. Fasting hypoglycemia : mnemonic EXPLAIN

- **E**xogenous drugs : insulin, oral hypoglycemic, alcohol.
- **P**ituitary insufficiency, hypothyroidism.
- **L**iver failure.
- **A**ddison's disease.
- **I**nsulinoma : tumor of pancreatic β cell that produce too much insulin.
- **N**on- pancreatic tumor(fibrosarcoma , mesothelioma) that produce Insulin like growth factor-I (IGF-1)

II. Postprandial (reactive) hypoglycemia :

- Alimentary hypoglycemia : gastrectomy. this is due to rapid glucose absorption with excessive insulin release $\Rightarrow$ glucose metabolized rapidly but insulin level remains high resulting in hypoglycemia.
- Idiopathic type.
- Early type II DM : The peak value of insulin occur after 2 hours or later when the absorption of CHO from the intestine has been completed.

Clinical picture : see hypoglycemic coma 5 & 5

Investigations :

- 1- Fasting plasma glucose : < 50 mg% in males , < 45 mg% in females.
- 2- Plasma level of insulin , thyroxin , cortisol.
- 3- The insulin / plasma glucose ratio : normally < 0.4 . It is higher in patients with insulinoma.

- 4- Liver & renal function tests.
- 5- Abdominal US & CT for tumors.

Treatment :

I. Fasting hypoglycemia :

- The acute attack : see hypoglycemic coma.
- Insulinoma : MCQ
 - Surgical removal .
 - Medical to prevent insulin release e.g. diazoxide , octreotide.

II. Postprandial hypoglycemia :

- Diet : Frequent small meals & avoid simple CHO.
- Drugs :
 - **P**robanthine : 7.5 mg 2 h before meals.
 - **P**henytoin : it inhibits insulin secretion.

We think so because all other people think so, or ... because we were told to think so, and think we must think so ...

Rudyard Kipling

Hirsutism

Definition : ↑↑ growth of body hair in androgen dependant areas.

Etiology :

a. Ovarian :

1. polycystic ovary syndrome > 90% of cases.
2. ovarian tumors secreting androgens.

b. Adrenal :

1. congenital adrenal hyperplasia (CAH).
2. Cushing's syndrome.

c. Drugs :

- | | |
|--------------|--------------|
| - minoxidil. | - phenytoin. |
| - androgens. | - diazoxide. |

Gynecomastia

Definition:

- Enlargement of the male breast, this is due to a decreased androgens : estrogen ratio.
- It should be differentiated from fatty breast which lacks the glandular element.
- It's unrelated to galactorrhea, breast enlargement is not necessary to make milk.

Etiology :

mnemonic : gynecomastia

- **G**enetic : Klinefelter syndrome
- **Y**oung boy (puberty)
- **N**eonate.
- **E**strogen.
- **C**irrhosis , cimetidine.
- **O**ld age.
- **M**arijuana.
- **A**cromegaly.
- **S**pirolactone.
- **T**umor (testis , adrenal & bronchogenic carcinoma)
- **I**NH.
- **A**lcoholism.

Obesity

Definition :

Obesity is an increase of body adipose (fat tissue) mass.

Etiology :

- Genetic factors.
- Excessive caloric intake.
- Diminished caloric consumption : physical inactivity.
- **Endocrinal :**
 - Cushing's syndrome.
 - Hypothyroidism.
 - Hypogonadism.
 - Insulinoma.
- Hypothalamic disorders : (DI , polyphagia , obesity , hypersomnia)
- Drugs : Cortisone , Contraceptive pills , Insulin , sulfonylureas , anti-psychotics.

Diagnosis of obesity :

- Body Mass Index (BMI) :

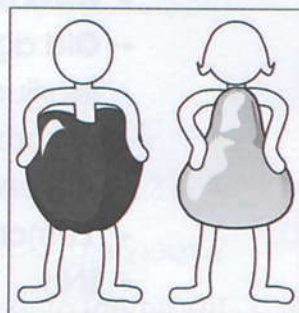
$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2(\text{m}^2)}$$

BMI	Classification
18.5 – 25	normal weight
25 – 30	overweight
30 – 35	class I obesity
35 – 40	class II obesity
Over 40	class III obesity

- **Skin fold thickness** e.g. over triceps (N : 20 mm in ♂ , 30 mm in ♀).

- Estimation of body fat : (Waist / hip ratio)

- a. Central obesity : more fat in the upper body (*Apple shaped*) , associated with more morbidity .
- b. Peripheral obesity : more fat in lower body (*pear shaped*) , associated with less morbidity .



Complications : (Hazards of obesity)**Cardiovascular :**

- Hypertension.
- Atherosclerosis & coronary heart diseases.
- DVT & pulmonary embolism.

Neurological :

- Stroke.
- Migraine.

Endocrinology :

- Type 2 DM.
- Menstrual disorders.

GIT :

- Cholecystitis & gall stones.
- Fatty liver.
- GERD.
- Hernias.

Respiratory :

- Dyspnea (restrictive hypoventilation)
- Sleep apnea syndrome.

Joints :

- Osteoarthritis.
- Back pain.
- Gout.

Psychological : depression & social stigmatization.

Malignancy : Increased incidence of : cancer colon , breast , prostate.

Metabolic syndrome : (syndrome X)

- Obesity.
- Hyperlipidemia.
- Hypertension.
- DM.

Treatment :

- Life style & diet modification : Low caloric , balanced diet with mild exercise.
- Drugs :
 - Orlistat (Xenical) : inhibits the pancreatic lipase so decrease fat absorption.
 - Sibutramine (Meridia) : Appetite suppressant.
- Surgery e.g. Gastric plication , liposuction : indicated with BMI > 40
- Treatment of the cause & complications.

Causes of precocious puberty

- In boys : puberty before age of 9 is considered precocious.
- In girls : Breast development or pubic hair with onset < 7 years.

I. Isosexual precocity :

a) **Central** : (Gonadotropin - dependent precocious puberty) :

- It is caused by premature activation of GnRH

- Causes :

- Idiopathic (constitutional).
- Hypothalamic hamartoma : produces pulsatile gonadotropin-releasing hormone (GnRH).
- Damage to the inhibitory system of the brain : due to infection, trauma, or irradiation.

b) **Peripheral** : (Gonadotropin - independent precocious puberty)

- Androgen from testis or adrenal gland is increased but gonadotropin is low.

- Causes :

- Congenital adrenal hyperplasia.
- Gonadal tumors (such as arrhenoblastoma)
- Adrenal tumors.
- Germ cell tumor.
- McCune–Albright syndrome : is a genetic disorder of bones, skin pigmentation and hormonal problems along with premature puberty.
- Exogenous sex steroid administration.

II. Heterosexual :

Refers to the premature development of estrogenic features in boys, such as breast development.

Diagnostic criteria of precocious puberty :

- Breast development in boys before appearance of pubic hair or testicular enlargement.
- Pubic hair or genital enlargement (gonadarche) in boys with onset before 9 years.
- Pubic hair (pubarche) before 8 or breast development (thelarche) in girls with onset before 7 years.
- Menstruation (menarche) in girls before 10 years.

Criteria & causes of delayed puberty

- In girls :
 - No breast development by 13 years, or
 - No menarche by 3 years after breast development (or by 16).
- In boys :
 - No testicular enlargement by 14 years,
 - Lack of pubic hair by age of 15, or
 - More than 5 years to complete genital enlargement.

Causes :

- a) Constitutional delay : it runs in families. (The most common)
- b) Systemic disease, e.g. chronic renal failure, thalassemia major.
- c) Undernutrition e.g. anorexia nervosa, zinc deficiency.
- d) Hypothalamic defects e.g. Kallmann syndrome, craniopharyngioma
- e) Pituitary defects e.g. hypopituitarism.
- f) Gonadal defects e.g. Turner syndrome, Klinefelter syndrome, Testicular failure due to mumps orchitis.
- g) Endocrine disorders e.g. hypothyroidism, Cushing's syndrome.

Loss of weight

Etiology :

I. Loss of weight inspite of good appetite :

- i. Increased caloric utilization :
 - Thyrotoxicosis.
 - Anexity.
 - Severe exercise.
- ii. Decreased intestinal absorption : malabsorption syndrome & diarrhea.
- iii. Diabetes mellitus.
- iv. Parasitic infection : Ascaris.

II. Loss of weight associated with decreased appetite :

- i. Psychological disorders :
 - Depression.
 - Anorexia nervosa.
- ii. Gastro-intestinal disorders : e.g.
 - Esophageal diseases.
 - Peptic ulcer.
 - Inflammatory bowel diseases.
 - Hepatobiliary diseases.
- iii. Systemic disorders : e.g.
 - Malignancy.
 - Cardiovascular diseases.
 - Infection.
- iv. Iatrogenic : Alcohol , Amphetamines : cause appetite suppression leading to weight loss.
- v. Smoking.

Endocrine syndromes affecting multiple glands

Multiple Endocrine Neoplasia (MEN)

MCQ

MEN-1 :

- Parathyroid adenoma.
- Pancreatic endocrine tumors : e.g. Gastrinoma, Insulinoma.
- Pituitary tumors : e.g. Prolactinoma, Acromegaly.

MEN-2A :

- Medullary carcinoma of thyroid.
- Pheochromocytoma.
- Hyperparathyroidism.

MEN-2B :

- Medullary carcinoma of thyroid. (100%) : *very aggressive with most patients.*
- Pheochromocytoma. (50%)
- Mucosal neuroma (100%) : painless nodules on the lips or tongue.
There may be enough neuromas in the body of the lips to produce enlargement and a "blubbery lip" appearance.

MCQ

Polyglandular Autoimmune Syndromes

- Association of multiple autoimmune endocrine disorders.
- There are 2 different syndromes :

Type I :

- **Characterized by triad of**
 - Mucocutaneous candidiasis.
 - Autoimmune hyperparathyroidism.
 - Adrenal failure.
- **Other autoimmune features :**
 - Primary hypogonadism.

- Autoimmune hypothyroidism.
- Alopecia.
- Autoimmune chronic hepatitis.
- Pernicious anemia.

Type II : more common

- Common features :

- Adrenal failure.
- Autoimmune thyroid disease e.g. Grave's disease.
- Type 1 DM.

- Other features :

- Primary hypogonadism.
- Myasthenia gravis.
- Pernicious anemia.
- Alopecia.
- Vitiligo.
- Celiac disease (gluten sensitive enteropathy).

First they ignore you, then they laugh at you, then they fight you, then you win.

Mahatma Gandhi

Dyslipidemia

- Dyslipidemia is elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis.

- Cholesterol & triglycerides are the major circulating lipid. Both are water insoluble & are transported in the blood stream as macromolecular complexes, called lipoproteins.

- Five principle types of lipoproteins are found in the blood :

1. Chylomicrons :

- Made by : the small intestines postprandially.
- Absorbed into: the lymph vessels, then --> moves into the blood.
- Rich in : TGs.
- Function : Deliver TG's to body cells to be used as fuel.

2. VLDL (Very Low Density Lipoproteins) :

- Made in : the liver from excess dietary carbohydrate and protein.
- Secreted into : the bloodstream.
- Rich in : TGs
- Function: Deliver TGs to body cells.

3. **IDL (Intermediate Density Lipoproteins)** : These are produced after removal of triglycerides from VLDL.

4. LDL (Low Density Lipoproteins) :

- Made in : the Liver as VLDL
- Arise from : VLDL once it has lost a lot of its TG's.
- Secreted into : the bloodstream.
- Rich in : Cholesterol (main carrier of cholesterol).
- Function : Deliver cholesterol to all body cells

5. HDL (High Density Lipoproteins) : " Healthy cholesterol "

- Made in : the Liver and Small Intestine.
- Secreted into : the bloodstream.
- Function : Pick up cholesterol from body cells and take it back to the liver "reverse cholesterol transport".
- Potential to help reverse heart disease.

Health risks of dyslipidemia :

1. There is a strong association between both total & LDL cholesterol concentration & coronary artery disease, peripheral vascular disease & cerebrovascular disease. Low HDL levels are also associated with increased cardiovascular risk.
2. Triglycerides levels more than 1000 mg/dl are associated with increased risk of acute pancreatitis.

Causes of dyslipidemia :

I. Primary causes :

Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL.

II. Secondary causes :

- Sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol & alcohol.
- Diabetes mellitus.
- Hypothyroidism.
- Nephrotic syndrome.
- Chronic renal failure & dialysis.
- Obstructive jaundice.
- Drugs : β blockers, Thiazides, estrogen, cortisone.

- **Diabetes** is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high LDL and low HDL.
- The cardiovascular risk in women with DM is similar to that of men.
- Patients with type 2 diabetes are especially at risk due to combination of obesity & poor control of diabetes.

Screening :

- Patients at risk should be screened e.g. presence of xanthelasma, obesity, DM, hypertension, acute pancreatitis, coronary artery disease, ...
- **Ideal levels :**

Total cholesterol	< 200 mg/dl
LDL cholesterol	< 100 mg/dl
HDL cholesterol	≥ 60 mg/dl
Triglycerides	< 150 mg/dl

Management :**I. General measures :**

- Treatment of secondary causes if possible.
- Dietary change : include decreasing intake of saturated fats and cholesterol, increasing the proportion of dietary fiber, and complex carbohydrates; and maintaining ideal body weight.
- Regular exercise.
- Needless to say stop smoking.

II. **Drugs** : are the next step when lifestyle changes are not effective.

A) If the predominant disturbance is cholesterol level :**🔪 Statins :**

- Lovastatin, Atrovastatin : 20-80 mg/d
- Statins inhibit hydroxymethyl-glutaryl CoA reductase, a key enzyme in cholesterol synthesis.
- Side effects : muscle toxicity & hepatotoxicity.

🔪 Cholesterol absorption inhibitors (e.g. ezetimibe) :

- Inhibit intestinal absorption of cholesterol.
- Side effects : diarrhea, abdominal pain, back pain.

- ✎ **Nicotinic acid** : inhibit lipid synthesis in the liver.
- ✎ **Bile acid binding resins** (Bile acid sequestrants)
e.g. cholestyramine. Safe in pregnancy.

B) If the predominant disturbance is triglyceride level :

- ✎ **Fibrates** :
 - e.g. gemfibrozil. They mainly promote lipoprotein lipase action.
 - Are drugs of choice, reduce TGs by about 50%.
- ✎ **Omega 3 fatty acids** : (marine fish oil)
 - o Reduce hepatic VLDL secretion
 - o Omega-3 fatty acids can be a useful adjunct to other therapies.
 - o Side effects : eructation and diarrhea

Collections of endocrine

Endocrinal emergencies :

- a. Diabetic comas.
- b. **Thyroid emergencies :**
 - i. Thyrotoxic crisis.
 - ii. Myxoedema coma.
- c. Parathyroid emergencies :
 - i. Acute hypercalcemia.
 - ii. Tetany.
- d. Adrenal crisis.

Endocrinal manifestations of systemic diseases :

- a. **Liver cell failure :** (↑ ADH & ↑ aldosterone)
 - i. In ♂ : gynecomastia , ♀ pubic hair , ↓ libido.
 - ii. In ♀ : breast atrophy , ♂ pubic hair , ↓ libido.
- b. **Chronic renal failure :**
 - i. 2ry & 3ry hyperparathyroidism.
 - ii. Hyperprolactinemia.
- c. **T.B. (miliary) :** Addison's disease.
- d. **Heamochromatosis :**
 - i. DM.
 - ii. Hypogonadism.
- e. **Sarcoidosis :**
 - i. DI.
 - ii. Addison's disease.
- f. **Malabsorption:** 2ry hyperparathyroidism.
- g. **Bronchogenic carcinoma, Hepatoma & hypernephroma :**
Endocrinal manifestations of paramalignant syndrome.

Endocrinal causes of HTN :

- a. Pituitary : acromegaly.
- b. Thyroid :
 - hypothyroidism → ↑ diastolic B.I.P.
 - hyperthyroidism → ↑ systolic B.I.P.
- c. Parathyroid : hyperparathyroidism.
- d. Pancreas : DM.
- e. Suprarenal : Conn's , Cushing syndrome, Pheochromocytoma.

Endocrinal causes of hyperlipidemia :

- a. Hypothyroidism.
- b. DM.
- c. Obesity.

Endocrinal causes of osteoporosis :

- a. DM.
- b. Hyperthyroidism.
- c. Hyperparathyroidism.
- d. Cushing syndrome.
- e. Osteomalacia.

Macro & micro-vascular complications of DM :

- a. Macro :
 - i. HTN.
 - ii. Atherosclerosis.
 - iii. Non healing ulcers & amputations.
- b. Micro : (Triopathy)
 - i. Retinopathy.
 - ii. Nephropathy.
 - iii. Neuropathy.

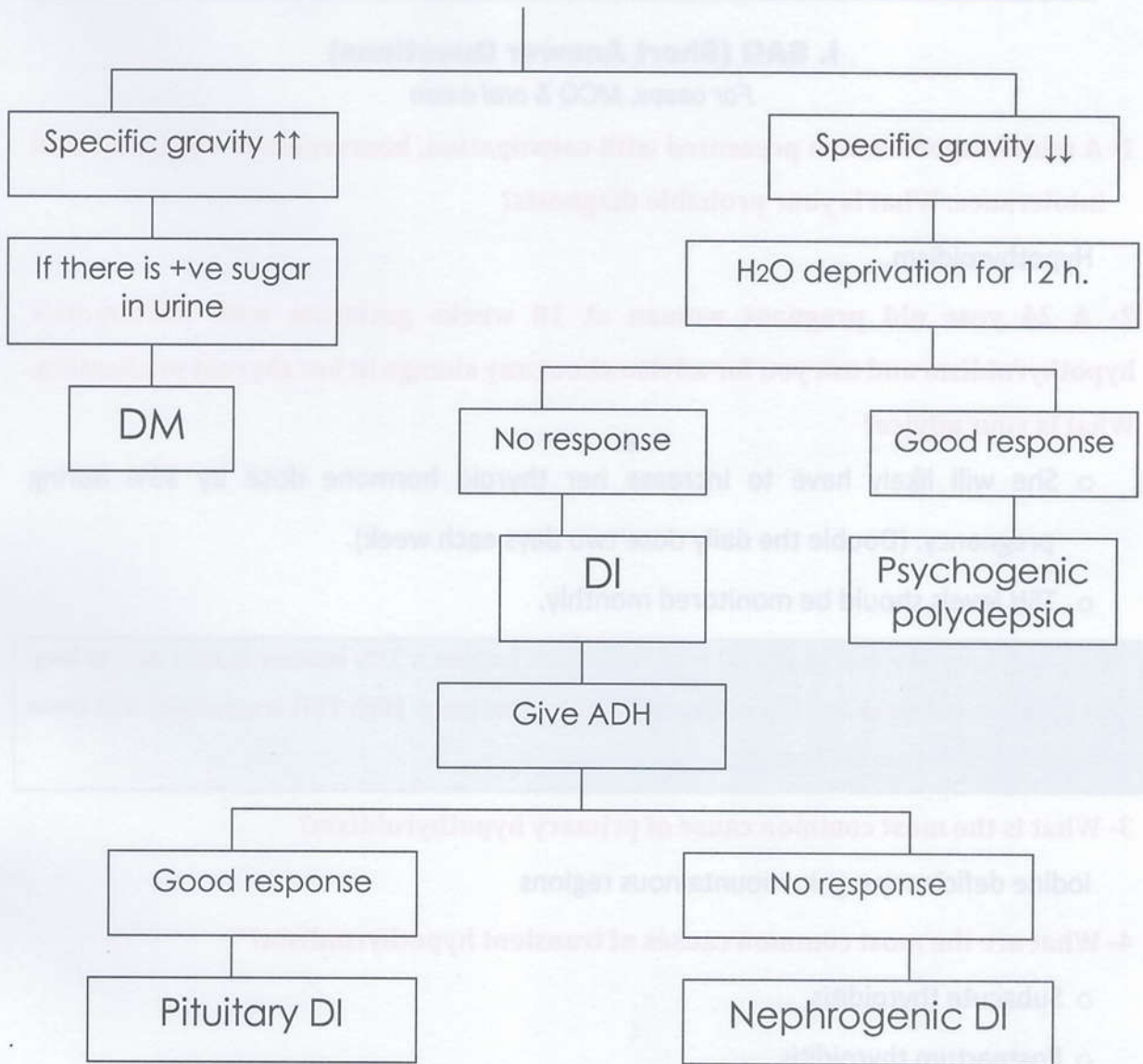
Immune mediated endocrinal diseases :

- a. Type 1 DM.
- b. Addison's disease.
- c. Grave's disease, Hashimoto thyroiditis.

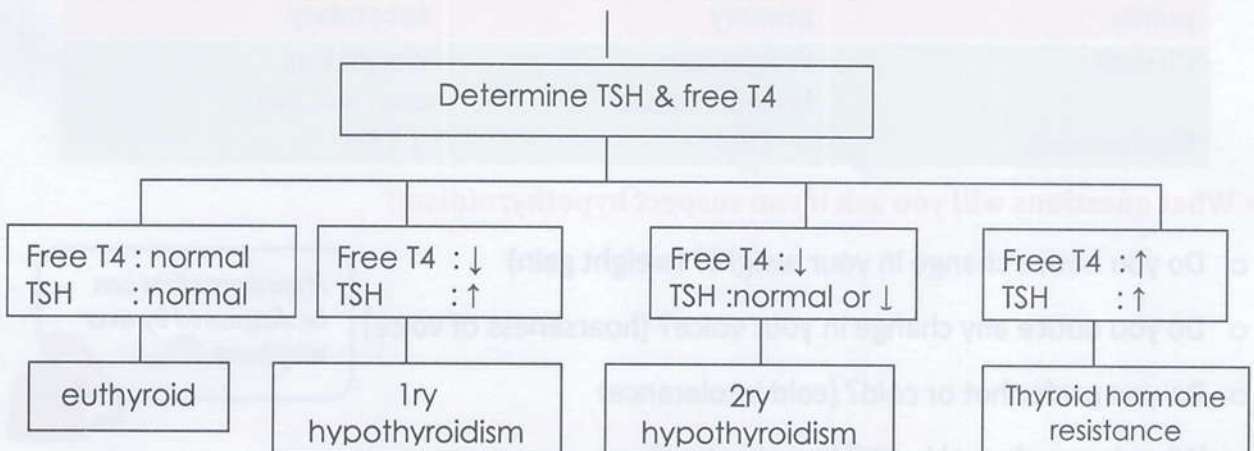
Iatrogenic endocrinal diseases :

- o Iodine → hyperthyroidism.
- o Lithium → hypothyroidism.
- o Amiodarone → thyroid dysfunction.
- o Ketoconazole → hyoadrenalism.
- o Metoclopramide → Hyperprolactinaemia.
- o Sympathomimetic → picture like thyrotoxicosis.
- o ACE s inhibitors → hypodosteronism.
- o Steroid therapy → DM & Cushing syndrome.
- o Thyroxin therapy → thyrotoxicosis (factitious).
- o Vitamin D → hypercalcemia.
- o Insulin & oral hypoglycemic → hypoglycemia.

Approach to patient with polyuria & polydipsia :



Approach to patient with hypothyroidism :



Endocrinology revision

I. SAQ (Short Answer Questions)

For cases, MCQ & oral exam

1- A middle aged woman presented with constipation, hoarseness of voice and cold intolerance. What is your probable diagnosis?

Hypothyroidism.

2- A 24 year old pregnant woman at 10 weeks gestation with Hashimoto's hypothyroidism and ask you for advice about any change in her thyroid medication. What is your advice?

- She will likely have to increase her thyroid hormone dose by 33% during pregnancy. (Double the daily dose two days each week).
- TSH levels should be monitored monthly.

During pregnancy, the dose of thyroid medication often requires a 33% increase in total dose to keep TSH within normal range and, if possible, in the low normal range. High TSH is associated with lower intelligence in the future for the child.

3- What is the most common cause of primary hypothyroidism?

Iodine deficiency e.g. in mountainous regions

4- What are the most common causes of transient hypothyroidism?

- Subacute thyroiditis
- Postpartum thyroiditis

5- How can you differentiate primary and secondary hypothyroidism?

points	primary	secondary
Clinically	Weight gain Myxedematous	Weight loss Lean and thin
Biochemically	↑ TSH	↓ TSH

6- What questions will you ask if you suspect hypothyroidism?

- Do you notice change in your weight? (weight gain)
- Do you notice any change in your voice? (hoarseness of voice)
- Do you prefer hot or cold? (cold intolerance)
- What is your bowel habit? (constipation)
- What is your menstrual history (in female only 😊)? Menorrhagia.

Hypothyroidism can be diagnosed by over telephone



7- If single investigation is asked for hypothyroidism, which one?

TSH

8- What are the ECG findings in hypothyroidism?

Sinus bradycardia with low voltage ECG

9- How will you treat the patient?

- Lifelong thyroxine therapy
- 50 µg (one tab.) daily for 3 weeks (given in morning in empty stomach) 100 µg for 3 weeks. Then maintenance dose at 100 – 150 µg daily. 6 weeks should pass before repeating thyroid function tests following a dose change.
- It is necessary to measure thyroid function every 1-2 years.

10- In which conditions initial small dose (25 µg) is used?

- Patients with IHD
- Elderly patient

11- What is myxedema madness?

Psychotic condition developed in a patient with hypothyroidism.

12- What are the clinical criteria of remission of hypothyroidism?

- Reduction of weight
- Decreased edema
- Relief of constipation
- Husky voice takes about 3-6 months to normalize.

13- What is the most common cause of hyperthyroidism?

Grave's disease

14- What are the common causes of transient hyperthyroidism?

- Subacute thyroiditis
- Postpartum thyroiditis

15- What is the pathogenesis of weight loss in hyperthyroidism?

Increased metabolic rate

16- What questions will you ask if you suspect hyperthyroidism?

- Do you notice any change in your weight? (weight loss)
- What is your appetite? (increased appetite)
- Do you prefer hot or cold? (hot intolerance)
- What is your bowel habit? (diarrhea)
- What is your menstrual history (in female only)? Scanty menses

17- Enumerate eye signs in hyperthyroidism?

See endocrinology book ... (mnemonic : **DR Must be Very Simple**)

18- What advice would you give to the patient on anti-thyroid drugs?

To seek immediate medical attention if they develop unexplained fever or sore throat (agranulocytosis, *baby*)

19- What are the clinical presentation of subacute thyroiditis (de Quervain thyroiditis)?

Viral upper respiratory infection followed by tender enlarged thyroid, can begin with hyperthyroid symptoms, then hypothyroid symptoms.

20- What are the possible side effect of radioactive iodine ablation?

- Hypothyroidism
- Thyrotoxic crisis secondary to the release of thyroid hormone into the blood.

21- What is the mortality rate of thyroid storm?

Up to 50%

22- What is subclinical hypothyroidism?

Elevated TSH levels but with normal thyroid hormone levels and with no clinical symptoms.

23- What is the most common type of thyroid cancer?

Papillary cancer

24- Which type of thyroid carcinoma is associated with MEN 2 & 3 (2B)?

Medullary cancer

25- Identify the TWO most common causes of hypercalcemia

- Primary hyperparathyroidism 55%
- Malignancy 30%

26- A 40 year old male presents with progressively worsening headache and sweating for 6 months. On query he admitted history of clash with door and bystander, increasing size of shoes and ring. What is your diagnosis?

Acromegaly

27- What is acromegaly?

It is a clinical condition characterized by hypersecretion of GH after closure of bony epiphysis. (acro means periphery, megaly means large)

28- What happens if it occurs before closure of epiphysis?

Gigantism

29- What is the initial investigation in a case of acromegaly?

IGF-1 confirmed by glucose suppression test

30- What is the explanation for raised prolactin level in a case of acromegaly?

It is explained by damage to pituitary stalk $\Rightarrow$ loss of inhibitory regulation of prolactin secretion by the hypothalamus. Plus prolactin & GH are secreted from acidophil cells of anterior pituitary.

31- Plain X-ray skull in a case of acromegaly. What about it?

- Widening of sella turcica and erosion of posterior clinoids.
- Widening of nasal sinuses.
- Prominent supraorbital ridges & occipital protuberance.
- Prognathism with wide separation of teeth.

32- What is the first line therapy in a case of acromegaly?

- Surgery : Transsphenoidal resection.
- Recently : Stereotactic surgery (stereotaxy) : minimally invasive form of surgical intervention with assistance of image guidance (MRI).
- Radiotherapy is the 2nd line therapy. Medical is the 3rd.

33- What malignancy are patients with acromegaly at increased risk for?

Cancer colon

34- What cranial nerve can be affected by prolactinoma?

Cranial nerve III

35- What is the Cushing's disease?

Cushing's syndrome due to pituitary cause e.g. pituitary adenoma

36- What are the most common cause of Cushing syndrome?

Exogenous corticosteroids

37- A patient with bronchial asthma was under good control with medication. He went to see his daughter far away from his house but forget to bring his medicines. Without medication he was free from breathless but in the next morning he developed nausea, vomiting, and collapsed. What is your diagnosis?

Adrenal crisis.

38- What is the finding of chest X-ray in Addison's disease?

Small heart (microcardia).

39- Mention some endocrinal emergencies?

- Hypoglycemia
- DKA
- Pituitary apoplexy
- Thyrotoxic crisis
- Myxedema coma
- Addisonian crisis
- Severe hypercalcemia

40- What are the presentation of DM?

- Asymptomatic : detected on routine investigation.
- Acute presentation with classic triad polyuria, polydipsia and polyphagia with weight loss.
- Non-specific symptoms : lack of energy, visual blurring, pruritis vulvae ...
- With complications : DKA, microangiopathy.

41- What are the early symptoms of DM?

- The three polys : polyuria, polydipsia & polyphagia with weight loss

42- What is the first line treatment for type 2 DM?

- Metformin

43- How can you differentiate hypoglycemic coma and DKA at bed side?

	HYPOGLYCEMIC COMA	DKA
History	○ No food ○ Vigorous exercise ○ Insulin overdose	○ Little or no insulin ○ Infection
Onset	○ In good previous health before the last insulin injection. ○ His GF usually brings him.	○ Ill health for several days ○ He comes with his wife
Symptoms	○ Palpitation, sweating, hunger	○ Polyuria, thirst, abdominal pain, vomiting
Signs	○ Moist skin and tongue ○ Full pulse ○ Normal or raised BP ○ Shallow or normal breathing ○ Hyperreflexia ○ No smell of acetone.	○ Dry skin and tongue ○ Weak pulse ○ Low BP ○ Rapid deep respiration ○ Diminished reflexes ○ Smell of acetone.

44- How can you differentiate between diabetic and hypertensive retinopathy?

	Diabetic retinopathy	Hypertensive retinopathy
Silver wiring (arteriolar thickening, tortuous, and increased reflectiveness.	Absent	Present
Arteriovenous nipping	Absent	Present
Hemorrhage	Dot and blot due to rupture of microaneurysms.	Flame-shaped
Papilledema	Absent	Present in grade 4
Neovascularization	Present in proliferative retinopathy.	Absent.

45- What type of fatal fungal infection can diabetic get?

- Mucor, especially sinusitis (Mucormycosis is a life-threatening fungal infection)

46- Mention three life threatening infections in diabetics.

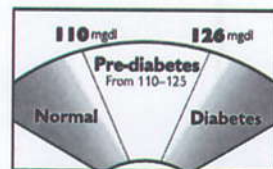
- ☒ Malignant otitis externa.
- ☒ Rhino-cerebral mucormycosis.
- ☒ Emphysematous cholecystitis.

47- What preventive measures are recommended to minimize diabetic complications?

- HgA1c < 7
- Lipid control : LDL < 70, TG < 150
- BP < 130/80
- Annual foot examination
- Check for proteinuria
- Annual funduscopy examination.

48- Criteria for diagnosis of prediabetes

- IFG (Impaired fasting glucose) : 100 – 125 mg% (5.6-6.9 mmol/L)
- IGT (Impaired glucose tolerance) : 140 – 199 mg% (7.8-11.0 mmol/L)
- Hb A1c : 5.7 – 6.4

**Prognosis :**

- ☒ IGT (impaired glucose tolerance) leads to type 2 DM in about 34% of cases over 5 Y.
- ☒ IGT & IFG together : lead to type 2 DM in 65% of cases.
- ☒ Prediabetics are at high risk for cardiovascular complications.

49- Diagnostic criteria of DM

Four ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day.

- A. FPG $\geq$ 126 mg/dL (7.0 mmol/L)
- B. 2-hr PG $\geq$ 200 mg/dL (11.1 mmol/L) during OGTT (75-g)
- C. A1C $\geq$ 6.5% (48 mmol/mol)
- D. Random PG $\geq$ 200 mg/dL (11.1 mmol/L) In individuals with symptoms of hyperglycemia e.g. polyuria, polydipsia,...

50- Genetic syndromes associated with diabetes

- Down's syndrome.
- Turner's syndrome.
- Friedreich's ataxia
- Myotonia dystrophy.

51- Why might severe headache, muscular inability, loss of consciousness and seizures occur with SIADH?

Cerebral edema associated with hyponatremia

52- What are the 4 hallmark characteristics of DI?

- Polyuria
- polydipsia
- dehydration
- hypernatremia

Enjoy!



II. Enumerate : written & oral

1. Features of polyglandular autoimmune syndrome (type 1 & 2)
2. Causes of Cushing syndrome. (ACTH dependent, ACTH independent)
3. Causes of secondary diabetes.
4. Causes of stunted growth (Dwarfism, short stature). P17
5. Endocrinal causes of short stature. P 17
6. Causes of hypercalcemia.
7. Causes of hypocalcemia.
 - Chronic renal failure.
 - Vitamin D deficiency.
 - Hypoparathyroidism.
 - Hyperphosphatemia.
 - Acute pancreatitis.
8. Causes of hypoglycemia in adult. Mnemonic : EXPLAIN
 - a) Exogenous drugs : insulin, oral hypoglycemic, alcohol
 - b) Pituitary insufficiency.....
 - c) Liver failure....
 - d) Addison's disease....
 - e) Islet cell tumor (insulinoma), Immune hypoglycemia (anti insulin receptor antibodies in Hodgkin's disease)
 - f) Non pancreatic neoplasm especially retroperitoneal fibrosarcoma.
9. Causes of hirsutism.
10. Causes of gynecomastia.
11. Causes of tetany.
12. Causes of hypoadrenalism.
13. Causes of hypothyroidism.
14. Causes of obesity.

15. Causes of loss of weight inspite of good appetite. P 116
16. Causes of nephrogenic DI.
17. Causes of Hyperprolactinemia. 3X5
18. Pharmacological causes of Hyperprolactinemia : 4 anti + others
19. Endocrinal causes of hypertension.
20. Side effect of metformin.
21. Endocrinal causes of abdominal pain.
22. Acquired causes of hyperlipidemia P120
23. Criteria for good diabetic control.
24. Laboratory tests for hyperthyroidism.
25. Acute diabetic complications : Coma, infection
26. Clinical stage of diabetic nephropathy
27. Skin complications of DM
28. Cardiovascular, neurological, urogenital complications of DM.
29. Causes of diarrhea in diabetes mellitus. ABCD
 - Autonomic neuropathy.
 - Bacterial overgrowth.
 - Celiac disease (autoimmune).
 - Drugs : e.g. metformin induced diarrhea.
30. Endocrinopathies ,that may be associated with hyperglycemia.
 - Acromegaly
 - Cushing's syndrome
 - Pheochromocytoma
 - Thyrotoxicosis.
 - Somatostatinoma, glucagonoma.

31- Causes of precocious & delayed puberty

III. GIVE A SHORT ACCOUNT ON

1. Management of DKA
2. Clinical picture & treatment of hypoglycemic coma.
3. Different types of insulin.
4. Indications, adverse effects of insulin.
5. Diabetic nephropathy.
6. Diabetic neuropathy
7. Microvascular complications of DM
 - Retinopathy - nephropathy - neuropathy
8. Oral hypoglycemic drugs
9. Management of type II diabetes (drug details needed)
10. Diagnosis , treatment of hyperthyroidism.
11. Diagnosis & treatment of hypothyroidism.
12. Thyroid emergencies
 - Thyrotoxic crisis (thyroid storm)
 - Myxedema coma
13. Clinical picture, investigations & treatment of primary hyperparathyroidism.
14. Management of Cushing's syndrome.
15. Causes, Clinical picture, Investigations & treatment of chronic adrenal failure.
16. Acute adrenal failure
17. Hazards of obesity.
18. Diagnosis, treatment of acromegaly.

19. Pituitary apoplexy.

- Def : sudden enlargement of the pituitary by hemorrhage into the tumor
- C/P :
 - Pressure manifestations : Headache , vomiting , visual defect.
 - Panhypopituitarism :
- Investigations :
 - Lab : evaluate pituitary hormones , electrolytes , glucose.
 - Imaging : CT , MRI (MRI is the most sensitive)
- TTT : Replacement therapy , Transsphenoidal surgical decompression of the tumor. *See panhypopituitarism*

20. Sheehan syndrome.**21. Management of tetany.****22. DD of polyuria.****23. DD of short stature.****24. DD of hypercalcemia.****25. DD of skin pigmentation.**

Smile!

It is only an exam!



Cases pearls

1- Acromegaly

- Adult
- Glove, ring, or shoe size : acutely ↑
- Coarsening of facial features, prognathism.
- Headache and visual affection.
- Dx : IGF-1, glucose suppression test, CT/MRI
- Tx :
 - Surgery is first choice.
 - Radiation is the 2nd.
 - Medical : somatostatin analogue.

Don't forget 5 endocrinal manifestations associated with acromegaly.

2- Prolactinoma :

- Headache, diplopia, CN III palsy.
- In male : Gynecomastia, impotence.
- In female : secondary amenorrhea, single with galactorrhea.
- Manifestations of panhypopituitarism may occur, *compression baby*.
- Etiology : 3 X 5 (5 physiological, 5 pharmacological, 5 pathological)
- Dx : CT/MRI, prolactin level > 250 ng/ml
- Ts : first line : dopamine agonist
- Large tumor or refractory : transsphenoidal surgery resection.

3- Sheehan syndrome (panhypopituitarism after sever postpartum hemorrhage)

- Female developed post partum hemorrhage, she could not lactate her baby
- General weakness and fatigability
- Dx :
 - Low thyroxin, cortisol, TSH, ACTH, FSH, LH
 - MRI is indicated to exclude mass lesion in pituitary gland
- Tx : Hrmone replacement. Don't forget Cortisone replacement before thyroxin.

4- Cushing's syndrome :

- Usually iatrogenic or due to pit. Adenoma (ACTH dependent, Cushing disease).
- Recently discovered DM
- Increased facial fullness (moon face) with truncal obesity.
- Hypertension.
- Lab : $\uparrow$ Na, $\downarrow$ K
- NB : Cushing with loss of weight, heavy smoker : consider paramalignant syndrome in a case of bronchogenic carcinoma.
- Dx: 24h urine cortisol and dexamethasone suppression test.
- Tx : surgical with postoperative cortisone replacement.
- Medical : mitotane, metayrapone, aminoglutethimide, ketoconazole.

5- Chronic adrenal failure :

- Usually female, suffers from easy fatigability, loss of weight.
- Skin pigmentation may occur in primary type.
- Hypoglycemia, hypotension
- $\downarrow$ Na, $\uparrow$ K, eosinophilia

Chronic adrenal failure + type 1 DM + thyroid disease = polyglandular syndrome type 2

- Dx : Low morning cortisol level $< 5 \mu\text{g/dl}$ is highly suggestive with ACTH stimulation test.
- Tx : 3 S (sugar, salt, steroid)

6- Acute adrenal failure

- As a complication of chronic adrenal failure in stress situations : infection, surgery
- Sudden withdrawal of cortisone : e.g. patient with SLE or bronchial asthma.
- Patient with panhypopituitarism : treated by thyroxin without cortisone.

7- Pheochromocytoma :

- Patient with acute onset episodes of hypertension, palpitation, flushing, sweating.
- Few months ago : his BP was normal
- Dx : ↑ catecholamine, CT adrenal
- Tx :
 - Surgical excision after preoperative α blocker
 - Ca channel blocker for hypertensive crisis
 - Combined α & β blockers for inoperable patients
 - Meta Iodo Benzyl Guanidine (MIBG) for metastatic disease.

8- Hyperthyroidism : Graves disease

- Young female.
- Diffuse painless goiter.
- Manifestations of hyperthyroidism : tachycardia, isolated systolic hypertension, atrial fibrillation, tremors, weight loss with ↑ appetite.
- Infiltrative ophthalmopathy & dermopathy (brawny pluritic hairy, non-pitting edema on the shins of tibia).
- Dx : ↓ TSH, ↑ free T4, T3, **TSI** (Thyroid stimulating immunoglobulin).

9- Subacute thyroiditis :

- Tender enlarged thyroid. Sometimes the pain can radiate to the jaw.
- Typically following viral upper respiratory infection (de Quervain's thyroiditis) or autoimmune (postpartum thyroiditis).
- It begins with hyperthyroid symptoms, then hypothyroid symptoms.
- Dx : elevated ESR, antithyroid antibodies in a case of postpartum thyroiditis (anti-thyroid peroxidase, anti-thyroglobulin Ab).
- Tx : typically self limited within weeks or months. Just cortisone or aspirin in severe cases & β blocker to decrease palpitation in some cases during hyperthyroidism phase.

10- Hypothyroidism :

- Female, obese, hypertensive, bradycardia, husky voice, constipation, mental slowness, puffy dull face with dry skin, thin lateral eyebrows.
- Pericardial effusion (increased cardiothoracic ratio) may occur.
- Causes include Hashimoto's thyroiditis and subacute thyroiditis.
- Dx : $\uparrow$ TSH, $\downarrow$ free T4 & T3. Antithyroid peroxidase Ab in Hashimoto's & postpartum thyroiditis.
- Tx : lifelong thyroxin in Hashimoto's thyroiditis.

11- Hyperparathyroidism :

- Hypercalcemia (N 8.5-10.5 mg %) and hypophosphatemia (N 2.5 – 5 mg %) & may be asymptomatic patient.
- C/P : Disease of bone, renal stone & others See endocrinology book

12 – Hypoparathyroidism :

- Chvostek's and Trousseau's signs are positive
- Paresthesia, tetany, seizures, muscle cramps.
- CT scan may reveal bilateral symmetrical basal ganglia calcification : chorea or parkinsonism are present in 20 - 30% of patients with basal ganglia calcification.
- Hypoparathyroidism is the most common cause of pathological basal ganglia calcification.
- Dx : low Ca, low PTH, $\uparrow$ phosphorus
- Tx : Ca and calcitriol (vitamin D) with follow up.

13- Diabetes mellitus : 4 scenarios

a. **Type 2 DM** : Obese patient, > 40 y, Classic triad (3Ps), HbA1c $> 6.5\%$

b. **Impaired glucose tolerance :**

- Patient (usually obese), presented with fasting glucose: 100 – 125 mg%, 2 H post-prandial 140 – 199 mg% or Hb A1c : 5.7 – 6.4%
- Many patients will progress to DM, recommend weight loss and exercise to prevent.

c. DKA :

- i. **DKA in DM type 1:** Young patient (e.g. 14 y), presented to ER with abdominal pain, repeated vomiting, polyuria and polydipsia in last month. Metabolic acidosis with increased AG, urine is positive for acetone.
- ii. **DKA in DM type 2 :** Poorly controlled DM type 2, with infection e.g. fatal fungal infection mucormycosis (blocked nose, facial pain, proptosis , vision loss).
- o Dignosis of DKA requires 3 things :
 - ✓ DM (type 1 or 2, but type 1 at higher risk)
 - ✓ Ketosis : blood & urine ketones, blood hydroxybutyrate
 - ✓ Acidosis : metabolic acidosis with **high anion gap**.

d. Diabetic nephropathy :

- o Long standing DM
- o Proteinuria.
- o Hypertension & the 3 microvascular complications (Retinopathy, neuropathy, nephropathy)
- o US kidney : Normal sized, hyperechogenicity.

BUT IT DOES MOVE ,,

GALILEO

Cases

1- Male patient of 42 years old, presented with parasthesia in his hands & feet of 6 months duration. During this period he was admitted to the emergency hospital with disturbed level of consciousness and left sided body weakness. He was fully investigated and received medical treatment and discharged well after one week. He advised to be kept on special diet regimen and specific drug (injection) used daily. He gave history of palpitation & fainting attacks on standing. Clinical examination revealed cachexia, white patches over the tongue. Pulse 98b/m, BP standing 140/85 and recumbent 180/105 mmHg. Heart accentuated S2 with ejection systolic murmur over the mitral area, Liver was enlarged 2 fingers with rounded border but not tender. Neurological examination revealed superficial & deep sensory affection.

- a) What is the provisional diagnosis ?
- b) Give an explanation to symptoms & signs in this patient.
- c) If there are other complications to the primary disease ?
- d) What is the pathogenesis of these complications ?
- e) What are the investigations suggested for diagnosis ?

a) This is a case of complicated DM and hypertension.

b)

- ✓ Peripheral neuropathy : parasthesia of hands & feet
- ✓ Autonomic neuropathy : fainting & postural hypotension & tachycardia.
- ✓ Monilial infection : white patches over the tongue.
- ✓ Accentuated S2 is due to hypertension
- ✓ Ejection systolic murmur is due to functional AS

c) complications of DM see endocrinology book

d) pathogenesis of DM & its complications

- ✓ Metabolic
- ✓ Recurrent infections.
- ✓ Vascular : micro & macro angiopathies
- ✓ Biochemical : accumulation of sorbitol $\Rightarrow$ neuropathy.

e) Investigations : see endocrinology book

2- Female patient aged 32 years presented with backaches and fatigability with polyuria. She was overweight. BP 140/100 mmHg. Fasting blood glucose 200mg%

- a) Mention 4 signs that help the diagnosis.
- b) What is the possible diagnosis and differential diagnosis ?
- c) How would you treat such case ?

a)

- ✓ Plethoric face.
- ✓ Hirsutism and acne may be apparent in female
- ✓ Pigmentation & purpura.
- ✓ Truncal obesity with stria rubra.
- ✓ Moon face : rounded face , bloated cheeks.
- ✓ Muscle wasting & weakness.

b)

Possible diagnosis : **Cushing's syndrome**

DD :

- ✓ Obese hypertensive diabetic patients.
- ✓ Female taking oral contraceptive pills.
- ✓ Chronic alcoholism.
- ✓ Frolich's syndrome : trunk obesity , hypogonadism , polyphagia.
- ✓ Differentiate between 1ry & 2ry Cushing. (.....)

c) Treatment of Cushing : see endocrinology book p 53

3- A 40-year-old man is seen because of headaches, muscle aches, and chronic low back and joint pain. As he enters the office, you notice his coarse facial features, frontal bossing, and large jaw. When you shake his hand, you find he has large, doughy, sweaty palms and, when he smiles, you note his teeth are widely spaced. He has not seen a physician in 10 years and is taking no medications. His back and joint pain have been worsening for 6 years, but his headaches started 6 months ago. His physical examination findings are significant for a BP of 150/100 mm Hg, pulse of 60 per minute, and respiratory rate of 12 per minute.

He returns in 2 weeks with old photographs that confirm a change in his physical appearance over time, and the laboratory test results confirm your clinical impression.

- a) What is your initial diagnosis in this patient?
- b) Besides the back and joint pain and the headaches, what other symptoms would you look for to confirm or refute your diagnosis?
- c) Besides the physical features you observe initially, what other abnormalities would you look for on physical examination?
- d) What laboratory tests should be performed initially?
- e) What additional testing should be performed once the initial laboratory results are known?
- f) What is the preferred treatment in this patient?

a) What is your initial diagnosis in this patient?

Acromegaly.

b) Besides the back and joint pain and the headaches, what other symptoms would you look for to confirm or refute your diagnosis?

Other symptoms to look for in this patient include a change in glove, ring, and shoe sizes, spaces between the teeth, decreased libido and impotence, sweating, new snoring, polyuria, polydipsia, and a change in vision.

c) Besides the physical features you observe initially, what other abnormalities would you look for on physical examination?

Other physical features to look for in this patient include thick coarse skin, enlarged extremities and organs, entrapment neuropathies, visual field abnormalities, and decreased body hair and testicular size. Old pictures would confirm the clinical suspicion.

d) What laboratory tests should be performed initially?

Initial laboratory tests in this patient would consist of the measurement of **IGF-1** (somatomedin C) and fasting GH levels. If the levels are elevated it would suggest the diagnosis of acromegaly, which would be confirmed if the GH levels did not suppress to less than 2 ng/mL in response to a glucose load (suppression test)

e) What additional testing should be performed once the initial laboratory results are known?

1. Investigations for the function of GH e.g. fasting blood sugar test should be performed to rule out diabetes.
2. Pituitary tests should include measurement of the prolactin, FSH, LH.
3. MRI scan can show the extent of the tumor, and formal visual field testing should be performed.
4. Echocardiography and colonoscopy should be performed to evaluate for cardiomegaly and colon polyps.

f) What is the preferred treatment in this patient?

1. The preferred initial treatment is surgical removal of the tumor.
 2. Bromocriptine or a somatostatin (octreotide) analog may be useful as medical adjuncts.
 3. Radiation therapy may be indicated for the destruction of residual tumor.
- Postoperative hormonal testing is indicated to reassess pituitary function.

4- A woman aged 50 years old, her weight is 95 kg & her height is 160 cm. She was discovered by chance to be diabetic.

- What are the laboratory criteria for diagnosis of DM?
- Discuss oral anti-diabetic drugs ?
- Describe one method by which you can know if she is obese.
- Enumerate the hazards of obesity.

The answer : Needless to say that she is **type 2 DM**

5- A 25 year old pregnant female developed severe post-partum hemorrhage which was successfully controlled. The baby was artificially fed as his mother's breast failed to secrete milk. The mother began to feel weak and she noticed atrophy of her breasts.

- What is the most probable diagnosis ?
- What is the expected BP of the patient ?
- How to prove your diagnosis by investigations ?

Three drugs were prescribed after the results of investigations were known, but the patient started only by one of them, in order not to distress her stomach. Next day the patient complained of severe abdominal colic, vomiting and diarrhea. Her BP was dropping rapidly and she became irritable and confused.

- What is your diagnosis ?
- How to manage the case ?

The answer :

- Sheehan syndrome.
- Acute adrenal failure.

6- A 60 year old woman comes to the emergency room in a coma. The patient's temperature is 35°C. She is bradycardiac. Her thyroid gland is enlarged. There is a bilateral hyporeflexia.

- What is the most probable diagnosis ?
- What are the clinical signs and symptoms you should look for in this patient ?
- What are the predisposing factors and what is the management of this case ?

a) Myxedema coma.

c) Predisposing factors : exposure to cold, infection, trauma, and CNS depressants.

7- A 42 years-old female presents with polyuria and polydipsia that proved to be due to diabetes mellitus diagnosed for the first time. The physician noticed enlargement of the hands and feet, deep voice, greasy skin, prognathism and enlargement of the tongue.

- What is the most probable diagnosis ?
- What are the investigations necessary to confirm your diagnosis ?
- What are the cardiovascular and neurological effects of the condition?
- What are the endocrinal changes of the condition ?
- What is the medical treatment of this patient ?

a) Acromegaly.

c) See endocrinology book

d) Endocrinal changes of acromegaly :

1- DM

2- Hyperprolactinemia : due to cosecretion from acidophils & pituitary stalk compression.

3- Hypogonadism due to hyperprolactinemia

4- Deficiency of other anterior pituitary hormones due to compression.

5- Deficiency of ADH (DI) : rare

MCQ

1- A 66 -year old man with type 2 diabetes notices painless skin lesions on his legs. They have an irregular raised border with a flat depressed center that is hyperpigmented brown in color. What is the most likely diagnosis?

- a) **Necrobiosis lipoidica.**
- b) Pyoderma gangrenosa.
- c) Erythema multiforme.
- d) Candidiasis.

2- Which of the following best describes the effect of propylthiouracil on thyroid hormone production?

- a) It inhibits uptake of iodide by thyroid cells.
- b) It blocks the release of hormones from the thyroid glands.
- c) It prevents the release of thyroid hormone from thyroglobulin.
- d) **It blocks iodination and coupling of tyrosine.**

3- A 53-year old woman with a past medical history of chronic kidney disease due to diabetic nephropathy is noted to have hyperphosphatemia & hypocalcemia. The disturbance is likely a result of metabolic bone disease seen in patients with chronic kidney disease. Which of the following findings is most likely associated with this electrolyte disturbance?

- a) Lethargy.
- b) **Neuromuscular irritability.**
- c) Anorexia, nausea and vomiting.
- d) Tachyarrhythmias.

4- Which of the following is the most common manifestation of multiple endocrine neoplasia, type 1 (MEN 1)?

- a) An adrenal adenoma.
- b) **Primary hyperparathyroidism.**
- c) Acromegaly.
- d) Islet cell tumor of the pancreas.

5- A 7-year- old boy has demineralized bones with pseudofractures seen on x-rays. Physiologic doses of vitamin D don't result in improvement. Which of the following is most likely to be associated with the syndrome?

- a) Hyperphosphatemia.
- b) Low vitamin D levels.
- c) **Alopecia**
- d) Mental retardation.

About 50% of cases of vitamin D-resistant rickets have alopecia. It is a familial disorder (X-linked recessive disorder).

6- Hyperthyroidism can be treated by all but which one of the following?

- a) **Triiodothyronine.**
- b) Iodide.
- c) Methimazole.
- d) Propylthiouracil.

Notice that Triiodothyronine is T₃, baby

- 7- Which of the following is the most likely metabolic effect of insulin on adipose tissue?
- a) Decrease in lipolysis.**
 - b) Decrease of glucose transport.
 - c) Decrease in lipoprotein lipase.
 - d) Decrease in glucose phosphorylation.
- 8- A 15-year- old youth has not gone through puberty. Which of the following is the most likely diagnosis?
- a) Inadequate diet.
 - b) Normal variation.**
 - c) Pituitary tumor.
 - d) Drug side effects.
- 9- Insulin is contraindicated in :
- a) Type 1 DM
 - b) Complicated type 2 DM
 - c) DM with pregnancy.
 - d) Hypoglycemic coma.**
- 10- Hypoglycemia is characterized by all the following EXCEPT
- a) Blurring of vision.
 - b) Headache.
 - c) Dry skin**
 - d) Pupillary dilatation.
- 11- Gynecomastia may be seen in all the following EXCEPT
- a) Newborn infants
 - b) Klinefelter's syndrome
 - c) Hypopituitarism.
 - d) Turner's syndrome**
- 12- Secretion of which of the following hormones does not primarily occur at night?
- a) Insulin**
 - b) Growth hormone
 - c) Melatonin
 - d) Prolactin
- 13- Earliest changes by ophthalmoscope in background retinopathy in diabetes
- a) Venous dilatation
 - b) Microaneurysms**
 - c) Increased capillary permeability
 - d) Arterio-venous shunts
- 14- Which is NOT a part of metabolic syndrome X
- a) Hyperlipidemia
 - b) Obesity
 - c) Ischemic heart disease**
 - d) Hypertension
- 15- Thiazolidinedione group of antidiabetic is
- a) Voglibose
 - b) Nateglinide
 - c) Rosiglitazone**
 - d) Glimepiride

16- All are features of diabetic ketoacidosis EXCEPT

- a) **Hyperthermia**
- b) Drowsiness
- c) Dehydration
- d) Air hunger

17- Commonest cause of coma in a diabetic is

- a) DKA
- b) Lactic acidosis
- c) Hyperosmolar hyperglycemic non ketotic coma
- d) **Hypoglycemia**

18- A patient of impaired fasting glucose ranges blood glucose value in between

- a) 96 - 106 mg/dL
- b) 106 - 116 mg/dL
- c) **100 - 125 mg/dL**
- d) 116 - 130 mg/dL

19- Microalbuminuria is urinary albumin excretion ratio between

- a) 10 - 20 $\mu\text{g}/\text{min}$
- b) **20 - 200 $\mu\text{g}/\text{min}$**
- c) 30 - 300 $\mu\text{g}/\text{min}$
- d) 40 - 400 $\mu\text{g}/\text{min}$

20- Myxedema coma is characterized by

- a) Hypertension
- b) Tachycardia
- c) Euthermia
- d) **Hypoventilation**

21- Thyrotoxicosis may be associated with all of the following EXCEPT

- a) Irritability
- b) **Constipation**
- c) Exophthalmos
- d) Tachycardia

22- Which cranial nerve is not involved in acromegaly

- a) VIII
- b) III, IV, VI
- c) **V**
- d) II

23- Pseudo-Cushing's syndrome may be found in all EXCEPT

- a) **Myxedema**
- b) Chronic alcoholism
- c) Obesity
- d) Depression.

24- Gynaecomastia may be produced after treatment with all EXCEPT

- a) Spironolactone
- b) Digitalis
- c) Cimetidine
- d) **Rifampicin**

25- Pheochromocytoma is not associated with

- a) **Weight gain**
- b) Fear of death
- c) Paroxysmal hypertension
- d) Constipation

26- A 27 year old female presenting with diarrhea, sweating & palpitation with diminished TSH & elevated T4. What is the next step in management?

- a) Thyroglobulin
- b) **RAIU scan**
- c) Thyroid antibodies
- d) Fine needle aspiration biopsy

Decreased TSH & elevated free T4 confirm a diagnosis of primary hyperthyroidism. The next best step is RAIU scan. If the RAIU scan reveals diffuse iodine uptake, then it is Graves (if it is homogeneously diffuse) or toxic multinodular (if it is heterogeneously diffuse).

27- Froehlich's syndrome is characterized by all EXCEPT

- a) Infantilism
- b) Truncal obesity
- c) **Diabetes mellitus**
- d) Mental retardation

28 - Which is not a part of multiple endocrine neoplasia type 1

- a) **Pheochromocytoma**
- b) Tumor of pituitary
- c) Tumor of pancreas
- d) Hyperparathyroidism

29- Tertiary hyperparathyroidism is commonly found in

- a) Rickets
- b) Pseudohypoparathyroidism
- c) **Chronic renal failure**
- d) Malabsorption syndrome

30- Commonest cause of thyrotoxicosis is

- a) Multinodular goiter
- b) Hashimoto's thyroiditis
- c) **Grave's disease**
- d) Well differentiated carcinoma

31- Osmoreceptors are present in

- a) Atria
- b) Kidney
- c) **Anterior hypothalamus**
- d) Adrenal cortex

32- In Somogyi phenomenon commonly associated with type 2 DM, the dose of insulin should be

- a) Increased
- b) Stopped
- c) **Decreased**
- d) Needs no change

33- Orlistat is used to treat

- a) Diabetic nephropathy
- b) Gout
- c) **Obesity**
- d) Anorexia nervosa.

34- Commonest cause of unilateral exophthalmos is :

- a) Cavernous sinus thrombosis.
- b) Retrobulbar tumor.
- c) Chloroma.
- d) **Thyrotoxicosis.**

35- Sleeping pulse rate is NOT increased in

- a) **Anxiety neurosis.**
- b) Rheumatic carditis.
- c) TB
- d) Atropinised patient.

36- Cardiovascular finding of thyrotoxicosis do not include

- a) Loud S1
- b) Means-Lerman scratch.
- c) Water hammer pulse.
- d) **Ejection click.**

Means-Lerman scratch is an uncommon type of heart murmur which occurs in patients with hyperthyroidism. It is a mid-systolic scratching sound best heard over the upper part of the sternum or second left intercostal space at the end of expiration. The murmur results from the rubbing of the pericardium against the pleura in the context of hyperdynamic circulation and tachycardia, and may mimic the sound of a pericardial rub.

37- Myxedema is characterized by all EXCEPT

- a) **Butterfly rash in face.**
- b) Sinus bradycardia.
- c) Solid edema.
- d) Madarosis.

Madarosis : hair loss of the eyebrows (superciliary madarosis) or loss of eyelashes (ciliary madarosis).

38- Acromegaly is associated with all of the following EXCEPT

- a) Acanthosis nigricans
- b) Fibromata mollusca
- c) **Micrognathia.**
- d) Cardiomegaly.

39- Klinefelter's syndrome is characterized by :

- a) Small, soft testes.
- b) Chromosomal pattern 46, XO
- c) Upper segment > lower segment of body.
- d) **Gynecomastia.**

40- Tall stature is NOT characteristic of

- a) Klinefelter's syndrome.
- b) Marfan's syndrome.
- c) Homocysteinuria.
- d) **Turner's syndrome.**

41- All of the following are featured by skin pigmentation EXCEPT

- a) **Conn's syndrome.**
- b) Bronchogenic carcinoma.
- c) Addison's disease.
- d) Hemochromatosis.

42- Medical adrenalectomy is done by all EXCEPT

- a) Aminoglutethimide.
- b) Mitotane.
- c) **Mexiletine.**
- d) Metyrapone.

43- Sheehan's syndrome presents with

- a) Cardiac failure.
- b) Persistent lactation.
- c) Fever
- d) Cachexia.**

44- Hypocalcemia is produced by all EXCEPT

- a) Hysterical hypoventilation.**
- b) Acute pancreatitis.
- c) Chronic renal failure.
- d) Osteomalacia.

45- Thyrotoxicosis may be featured by all EXCEPT

- a) Myopathy
- b) Pretibial myxedema.
- c) Hypernatremia.**
- d) Atrial fibrillation.

46- Hyperparathyroidism is NOT featured by

- a) Acute pancreatitis.
- b) Nephrocalcinosis.
- c) Palpable neck swelling.**
- d) Pseudogout.

47- Malignant hypercalcemia is treated by all EXCEPT

- a) Pamidronate.
 - b) Calcitonin
 - c) Calcitriol**
 - d) Glucocorticoids.
- Calcitriol (active vit D)

48- Commonest cause of Addison's disease is

- a) Granuloma
- b) Idiopathic atrophy**
- c) Inflammatory necrosis.
- d) Malignancy

49- Moon face is characteristic of :

- a) Addison's disease
- b) Cushing' disease**
- c) Sjogren's syndrome
- d) Simmond's disease

50- Features of Addison's disease do not include

- a) Diarrhea
- b) Dizziness
- c) Dermatitis**
- d) Dehydration.

51- Addison's disease is characterized by all of the following EXCEPT :

- a) Skin pigmentation
- b) Asthenia
- c) Hypokalemia**
- d) Hypotension

52- Otitis fibrosa cystica is associated with

- a) Addison's disease
- b) Hypothyroidism
- c) Hyperparathyroidism**
- d) Hyperthyroidism

53- All of the following are side effects of prolonged use of cortisone EXCEPT

- a) Anemia**
- b) Growth retardation
- c) Muscle wasting
- d) Increased susceptibility to infection

54- Glycated fructosamine gives an indication of glycemia control for last

- a) 1 month
- b) 3 months
- c) 3 days
- d) 14 days**
- Fructosamine levels typically reflect albumin glycation. Because albumin has a half-life of 20 days, the plasma fructosamine concentration reflects relatively recent (up to 2 weeks) changes in blood glucose.
- It is rarely used in clinical practice (hemoglobin A1c testing are preferred).
- Notice that glycated hemoglobin (HbA1c) measures average glucose levels over 3 months.

55- Confirmatory evidence of growth hormone deficiency is documented by

- a) CT scan
- b) Low IGF-1
- c) Low growth hormone levels after provocative tests**
- d) Delayed bone age

56- Insulin requirements for diabetes are reduced in :

- a) Infections
- b) Exercise**
- c) Emotional stress
- d) Hyperthyroidism

57- All are causes of hyperprolactinemia except :

- a) Bromocriptine**
- b) Phenothiazine
- c) Methyldopa
- d) Metoclopramide

58- Which drug is essential in Sheehan's syndrome :

- a) Estrogen
- b) Cortisone**
- c) Thyroxin
- d) Growth hormone

59- Addison's disease is characterized by following except-

- a. Hyperkalemia
- b. Hypotension
- c. Hyponatremia
- d. Hypocalcemia**

60- All of the following statements about Hashimoto's disease are true except:

- a) Many patients are entirely asymptomatic
- b) Not all patients become hypothyroid
- c) Most cases of obesity are attributable to Hashimoto's disease**
- d) Hypothyroidism may be subclinical

Although weight gain may be a symptom of Hashimoto's disease, the majority of obese people have normal thyroid function.

61- The most common benign tumor of the pituitary gland is :

- a) Glioma
- b) Prolactinoma**
- c) Carcinoid tumor
- d) Islet cell tumor

62- Thyroid acropachy is found in :

- a) Subclinical hypothyroidism
- b) Grave's disease**
- c) Myxedema
- d) Medullary carcinoma of thyroid

63- Causes of short stature in childhood include EXCEPT :

- a) Klinefelter's syndrome**
- b) Turner's syndrome
- c) Cushing's syndrome
- d) Primary hypothyroidism

64- Adverse effects of oral corticosteroid therapy include EXCEPT

- a) Peptic ulcer
- b) Hypertension
- c) Avascular bone necrosis
- d) Pseudo-gout**
- e) Insomnia

Cortisone sometimes used to treat severe pseudo-gout

65- As regard to thyrotoxicosis, which is incorrect?

- a) Grave's disease is the most common cause
- b) Uninodular goiter is more common than multinodular goiter**
- c) Amiodarone therapy is occasionally responsible
- d) The thyroid gland is diffusely hyperactive in Grave's disease
- e) There is an increased prevalence of HLA DR3 in Grave's disease

66- Causes of hypercalcemia include EXCEPT :

- a) Carcinomas secreting PTH like peptides
- b) Severe Addison's disease
- c) Severe hypothyroidism**
- d) Chronic sarcoidosis

67- Calcium level in the blood is regulated by :

- a) Parathyroid and thyroid**
- b) Adrenal medulla and pancreas
- c) Testis
- d) Parathyroid and thymus

68- In a case of Graves disease, Which of the following is a possible side effect of RAI treatment?

- a) Agranulocytosis.
- b) Recurrent laryngeal nerve injury
- c) Worsening of Graves ophthalmopathy**
- d) Cholestasis

With RAI treatment, iodine concentrates in the follicular cells of the thyroid & ablates them completely within 2 to 4 months. It will not decrease circulating levels of TSH receptor antibodies, so it will not treat Graves ophthalmopathy. Through an unclear mechanism, it can actually worsen ophthalmopathy. In order to prevent this, some doctors give cortisone prior to RAI treatment.

69- Karyotype 47, XYY is

- a) True hermaphroditism
- b) Supermale**
- c) Klinefelter's syndrome.
- d) Gonadal dysgenesis.

70- A 54 year old woman with a history of type 1 DM and autoimmune thyroid disease presents with weakness, anorexia, nausea and vomiting. She has a BP of 82/64 mmHg and physical examination reveals spotty hyperpigmentation of her mucous membranes in her oral cavity. Laboratory results reveal K of 6.1 mEq/L and elevated ACTH level. Which of the following is the underlying diagnosis in this patient?

- a) MEN 1
- b) MEN 2
- c) Polyglandular autoimmune syndrome type 1
- d) Polyglandular autoimmune syndrome type 2**

71- As regard to thyroid nodule, which of the following features is NOT associated with an increased risk of malignancy?

- a) Hard and immobile mass
- b) Cold nodule on RAIU
- c) Cervical lymphadenopathy
- d) **Hot nodule on RAIU**

72- Type of insulin best used for treatment of diabetic ketoacidosis

- a) **Crystalline insulin**
- b) NPH insulin
- c) Lente insulin
- d) A and b
- e) A and c

73- Symptoms of Grave's ophthalmopathy include all of the following except:

- a) Bulging eyeballs
- b) Dry, irritated eyes and puffy eyelids
- c) **Cataracts**
- d) Light sensitivity

74- Which one of the following inhibits growth hormone secretion from the anterior pituitary gland?

- a. **Somatostatin.**
- b. GH releasing hormone.
- c. Hypoglycemia.
- d. Arginine.
- e. Serotonin.

GHRH, Hypoglycemia, insulin, arginine, serotonin $\rightarrow \uparrow$ GH.

75- In hypertensive individual, which one of the following is the likely finding in a patient with renal artery stenosis and is helpful in distinguishing the condition from Conn's syndrome?

- a. A high aldosterone level
- b. A high renin and a low aldosterone level.
- c. **A high renin level**
- d. A low aldosterone level
- e. A low renin and a high aldosterone.

Renal artery stenosis results in high renin and high aldosterone levels in contrast to Conn's syndrome in which the aldosterone level is high but the renin is characteristically suppressed.

76- A 45-year-old obese man without known medical problems complains of feeling very sleepy during the day and often falling asleep while listening to friends. The most likely cause of this patient's problem is

- a. narcolepsy
- b. **upper airway obstruction at night**
- c. glucocorticoid excess
- d. growth hormone excess
- e. estrogen excess

77- Obese persons are at an increased risk for which of the following disorders?

- a. Hypothyroidism
- b. **Cholelithiasis**
- c. Type 1 diabetes mellitus
- d. Elevated levels of HDL cholesterol

78- Which of the following regimens is best for the preoperative management of a patient with a known pheochromocytoma?

- a. Propranolol alone
- b. Propranolol followed by phenoxybenzamine
- c. **Phenoxybenzamine followed by propranolol**
- d. Prazosin alone
- e. Propranolol followed by prazosin

79- Which of the following may be a direct consequence of severe magnesium deficiency?

- a. Hypophosphatemia
- b. Hypercalcemia
- c. **Hypokalemia**
- d. Hyponatremia
- e. Shortening of the QT interval

80- A 55-year-old woman presents to her physician with mild fatigue. Her past medical history is unremarkable. She is taking no medication. No abnormalities are detected on physical examination. The only abnormality detected on routine blood testing is an elevated calcium (11.9 mg/dL) and a serum inorganic phosphorus of (2 mg/dL). An immunoreactive parathyroid hormone level is undetectable. The most likely etiology for this patient's high serum calcium is

- a. primary hyperparathyroidism
- b. **malignancy**
- c. hypervitaminosis
- d. hyperthyroidism
- e. familial hypocalciuric hypercalcemia

hypercalcemia and hypophosphatemia without elevated levels of PTH are likely to have the hypercalcemia of malignancy. Patients with excessive levels of vitamin D would not be expected to have a low serum phosphate. Second, patients with familial hypocalciuric hypercalcemia, an autosomal dominant trait, often have normal or slightly low levels of immunoreactive parathyroid hormone. It is now clearly recognized that many solid tumors, including carcinomas of the lung and kidney, may produce (PTH like) that will not be identified by the currently available assays that detect true parathyroid hormone elaborated from the parathyroid gland.

81- The most common presentation of primary hyperparathyroidism is

- a. bone fracture
- b. increased serum creatinine
- c. osteitis fibrosa cystica
- d. calcium kidney stones
- e. **asymptomatic hypercalcemia**

82- Which of the following medications is known to cause hyperprolactinemia?

- a. **Metoclopramide**
- b. Levothyroxine
- c. Glucocorticoids
- d. Propranolol
- e. Cigarette use

83- A 23-year-old woman is diagnosed with Graves' disease shortly after discovering she is pregnant. Appropriate therapy includes

- a. radioactive iodine to ablate her thyroid gland
- b. propylthiouracil with the goal of maintaining her thyroid function tests in slightly high range.
- c. methimazole therapy
- d. a beta blocker
- e. propylthiouracil with care taken to maintain her thyroid function tests in the mid normal range

Radioactive iodine should never be given to a pregnant woman. In addition, both methimazole and beta blockers should be avoided in pregnant women. Antithyroid drugs, including propylthiouracil, cross the placenta and affect fetal thyroid function. Studies have shown that when a treated pregnant woman's thyroid function is in the mid-normal range, the fetus is hypothyroid. When the mother's thyroid tests are maintained in the high-normal or slightly hyperthyroid range, the fetus is likely to have normal thyroid function.

84- A 19-year-old man with type 1 diabetes mellitus presents to the emergency room with nausea and vomiting. His arterial pH is 7.16 with potassium of 5.4 mEq/L, bicarbonate of 7 mEq/L, sodium of 132 mEq/L, phosphate of 3.0 mg/dL, and glucose of 475 mg/dL. In addition to intravenous saline & insulin, which electrolyte should be considered in treatment of this case?

- a. Bicarbonate
- b. **Potassium**
- c. Dextrose
- d. Phosphate
- e. None of the above

The mainstay of therapy for diabetic ketoacidosis (DKA) is insulin and intravenous fluids.

DKA cannot be reversed without insulin. Although the serum K concentration is high, the K concentration will drop quickly due to insulin therapy (due to intracellular shift).

Because glucose levels drop more quickly than ketones disappear from the plasma, it is usually necessary to give intravenous dextrose when the blood glucose level drops below about (250 to 300 mg/dL). This allows continued administration of insulin to clear the ketones from the blood. Bicarbonate therapy is not recommended unless the arterial pH falls below 7.10 or 7.00 because the rapid alkalization may impair oxygen delivery to tissues and impair left ventricular function. In addition, insulin therapy is effective in reversing the acidemia without the assistance of bicarbonate therapy.

85- The diagnosis of diabetes mellitus is certain in which of the following situations?

- a. Abnormal oral glucose tolerance in a 24-year-old woman who has been dieting
- b. **Successive fasting plasma glucose 147, 165, and 152 mg/dL in an asymptomatic woman**
- c. A serum glucose level 100 mg/dL in a woman in her twenty-fifth week of gestation after a 50 g oral glucose load
- d. Persistent asymptomatic glycosuria in a 30-year-old woman
- e. Persistently elevated nonfasting serum glucose levels

Persistent fasting hyperglycemia even if it is asymptomatic, has been recommended by the National Diabetes Data Group as a criterion for the diagnosis of diabetes.

Abnormal glucose tolerance—whether after eating or after a standard “glucose tolerance test”—can be caused by many factors (e.g., anxiety, infection or other illness). Similarly, glycosuria may have renal as well as endocrinologic causes. Therefore, these two conditions cannot be considered diagnostic of diabetes. Gestational diabetes is diagnosed in women between the 24 – 28 weeks of gestation, first using a 50-g oral glucose load, if the 1-h glucose level 140 mg/dL; a 100-g oral glucose test is performed after an overnight fast. Gestational diabetes is initially treated with dietary measures; if the postprandial glucose level remains elevated, insulin therapy is often started. About 30% of women with gestational diabetes will eventually develop true DM.

86- A 46-year-old woman arrives in your clinic for routine examination. She has no specific complaints, and a full review of systems is unrevealing. On physical examination she has normal vital signs and a 1.5 cm thyroid nodule is palpated in the right lobe of her thyroid; there are no other abnormal findings. A laboratory test reveals a serum TSH level of 2.3 mU/L. Which of the following would be the most appropriate recommendation?

- a. **Fine-needle aspiration biopsy**
- b. Unilateral thyroid lobectomy
- c. Thyroxine suppressive therapy
- d. Radioiodine therapy
- e. No intervention needed; a wait and watch approach is recommended

87- Which of the following has been associated with an effective approach towards the prevention of diabetic retinopathy?

- a. A reduction in the serum triglyceride level
- b. **Improved control of blood glucose concentrations**
- c. Use of an ACE inhibitor
- d. Use of aspirin therapy
- e. Smoking cessation

88- Which of the following medications is known to cause hypoglycemia?

- a. Acetaminophen
- b. **Pentamidine**
- c. Epinephrine
- d. Verapamil
- e. Thiazides

Insulin, sulfonylureas, disopyramide, and pentamidine (Antiprotozoal) all cause hypoglycemia through hyperinsulinemia. Thiazides can cause hyperglycemia. Acetaminophen when taken in normal dosages does not affect the serum glucose concentration; however, an overdose causing hepatic damage could lead to severe hypoglycemia.

89- Causes of fasting hypoglycemia that are due primarily to overutilization of glucose include

- a. acromegaly
- b. **hepatoma**
- c. alcohol ingestion
- d. congestive heart failure from cor pulmonale
- e. Hypopituitarism

90- Manifestations of hypothyroidism include

- a. prolongation of the QT interval
- b. depressed serum cholesterol
- c. **increased serum creatine phosphokinase**
- d. decreased serum lactate dehydrogenase level

91- Which of the following is most sensitive for detecting diabetic nephropathy?

- a. Serum creatinine level
- b. Creatinine clearance
- c. **Urine albumin**
- d. Glucose tolerance test
- e. Ultrasonography

92- Which of the following statements regarding adrenal insufficiency is true?

- a. The most common cause of adrenal insufficiency is tuberculosis
- b. The critical test for the diagnosis of chronic adrenal insufficiency is Synthetic ACTH test
- c. ACTH levels greater than normal in secondary adrenal insufficiency.
- d. 2ry adrenal insufficiency is characterized by skin pigmentation.

93- Which of the following statements regarding hyperaldosteronism is true?

- a. The most common causes of secondary hyperaldosteronism are congestive heart failure and cirrhosis with ascites
- b. Treatment of primary adrenal hyperaldosteronism is spironolactone
- c. Patients with primary adrenal hyperaldosteronism usually present with hypertension, hypokalemia, and metabolic acidosis
- d. Diagnosis of primary adrenal hyperaldosteronism is confirmed by elevations in the levels of both renin and aldosterone
- e. Patients with primary adrenal hyperaldosteronism usually present with generalized edema.

Primary hyperaldosteronism is caused by benign adrenal adenomas, which are typically unilateral and are usually less than 2.5 cm in diameter. Patients present with mild hypertension without edema due to renal escape phenomenon. Laboratory testing shows hypernatremia, hypokalemia and metabolic alkalosis not acidosis. Diagnosis is confirmed by elevated plasma aldosterone levels (> 14 ng/dl) & suppressed plasma renin activity. The treatment of primary hyperaldosteronism is unilateral adrenalectomy, preferably by a laparoscopic procedure. Secondary hyperaldosteronism may or may not be associated with hypertension.

94- A 42-year-old man with long-standing type 1 diabetes presents with gastroenteritis that has been worsening for 5 days. His blood pressure is 90/55 mm Hg, and his heart rate is 135 beats/min. Other laboratory findings are as follows: blood glucose: 656 mg/dl; sodium: 127 mEq/L; potassium, 4.2 mEq/L; HCO_3^- : 14 mEq/L; anion gap, 25; and pH, 7.05. Which of the following would not be an appropriate step in the immediate treatment of this patient?

- a. I.V. administration of 0.9% saline
- b. Admission to the intensive care unit
- c. I.V. administration of potassium chloride
- d. I.V. administration of insulin
- e. I.V. administration of sodium bicarbonate

Administration of bicarbonate is not generally required in most cases of DKA and is generally reserved for treatment of severe acidosis ($\text{pH} < 7.0$ or $\text{HCO}_3^- < 10$)

95- As regard to secondary diabetes, which is correct ?

- a. A patient can be assumed not to be ketosis-prone
- b. Most patients with panhypopituitarism are diabetic
- c. Classical diabetic complications do not occur
- d. **Thiazide diuretics and beta-blockers can both impair insulin secretion**
- e. Most patients with acromegaly are diabetic

Secondary diabetes causes all the same complications as primary diabetes, including DKA.
15% of patients with acromegaly are diabetic.

96- The physiological effects of insulin include

- a. **increased glycolysis**
- b. increased glycogenolysis
- c. increased lipolysis
- d. increased gluconeogenesis
- e. increased protein catabolism

97- The most likely etiology for the eating disorder anorexia nervosa is

- a. decreased levels of luteinizing hormone– releasing hormone (LHRH)
- b. decreased levels of growth hormone
- c. decreased levels of insulin-like growth factor I
- d. low levels of serum thyroxine
- e. **psychiatric disorder**

98- Which of the following is most likely to be associated with increased insulin sensitivity?

- a. Acromegaly
- b. Smoking cessation
- c. Pheochromocytoma
- d. Polycystic ovary disease
- e. **Weight loss**

99- In metabolic diabetic ketoacidosis (DKA), the treatment of choice is :

- a. Normal saline , IV insulin , metformin.
- b. **Normal saline , IV insulin , potassium**
- c. Normal saline , insulin , heparin
- d. Normal saline , IV insulin , cortisone
- e. IV 5% glucose.

100- In Cushing syndrome which of the following is true ?

- a. **Esinopenia**
- b. Basophilia
- c. Esinophilia
- d. Lymphocytosis
- e. Neutropenia

101- Syndrome of inappropriate ADH secretion may result from EXCEPT :

- a. Meningitis
- b. Bronchial carcinoma
- c. **Digoxin therapy**
- d. Head injury
- e. Pneumonia

102- Causes of DI include the following EXCEPT :

- a. Congenital disorder
- b. Craniopharyngioma
- c. DIDMOAD syndrome
- d. **Severe hypocalcemia**
- e. Sarcoidosis

103- Which of the following test would most reliably defect a deficiency of the GH axis in a 19 year-old man ?

- a. ACTH stimulation test
- b. Arginine test
- c. Glucose test
- d. **Insulin tolerance test**
- e. TRH administration test

104- Causes of nephrogenic DI include the following EXCEPT :

- a. Lithium
- b. Hypokalemia
- c. Congenital disorder
- d. **Chlorpropamide & carbamazepine therapy**
- e. Renal amyloidosis

105- A 20 year old lady with a six month history of sweating and diarrhea . She is otherwise well. Her father and grandmother died in middle age but she is unsure of the reason why. On examination, no abnormality could be found. Which one of the following diagnoses would it be important to exclude?

- a. Cushing's disease
- b. Grave's disease
- c. Acromegaly
- d. **Medullary thyroid carcinoma**

Medullary thyroid carcinoma (MTC) can secrete a variety of peptides and prostaglandins, resulting in extra-thyroid symptoms. Diarrhea and sweating are the most common. It is an important tumor to exclude since it can metastasise early. MTC can be inherited as part of MEN type 2.

Acromegaly can also cause sweating due to sweat gland hypertrophy , but usually not diarrhea. Cushing's disease also rarely presents with these symptoms. Both these conditions also rarely show such strong family history

106- A patient comes in for a fasting plasma glucose test .On two separate occasion , the result has been 115 and 120 mg/dl which of the following is the most appropriate next step ?

- a. Reassurance that these are normal blood sugar
- b. **Recommend weight loss and exercise.**
- c. Diagnose DM and start a sulfonylurea agent
- d. Recommend cardiac stress test
- e. Hospitalize him urgency

107- A 45 year-old obese woman presents for follow up of her diabetes. She currently take glipizide (sulfonylurea) 10 mg twice per day, and her fasting morning glucose is 180 mg/dl. Her last HbA1c was 7.9 . She states that she conscientiously follows her diet and that she walks 45 minutes daily. What is the best next step in her care ?

- a. Add an insulin pump
- b. **Add metformin**
- c. Hospitalize her urgency
- d. Add antibiotic

108- The finding of reduced free T4 & TSH is compatible with :

- a. **Hypopituitarism**
- b. 1ry hypothyroidism
- c. Nephrotic syndrome
- d. 2ry hyperthyroidism

109- A 33-year old woman is noted to have Grave's disease .Which of the following is the best therapy ?

- a. Long term propranolol.
- b. Lifelong oral propylthiouracil (PTU)
- c. **Radioactive iodine ablation**
- d. Surgical thyroidectomy

It is the definitive treatment for Grave's disease. Surgery is indicated for obstructive symptoms or for women during pregnancy.

110- In 1ry hyperaldosteronism (Conn's syndrome) ...

- a. peripheral edema is usually present
- b. **proximal myopathy is due to hypokalemia**
- c. severe hypertension is characteristic
- d. DM is often present
- e. hypertension is associated with hyperreninemia

Now, and after your journey with Endocrinology ... REMEMBER that ..



Everyone likes her to be Hot & Cystic ... NOT ... Cold & Solid

I'm talking about thyroid nodule

- Hot nodule by thyroid scan & cystic by US : benign nodule.
- Cold nodule : 15% malignant.



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